SEP-363856

Clinical Study Protocol SEP361-302

A Randomized, Double-blind, Parallel-group, Placebo-controlled, Fixed-dose, Multicenter Study to Evaluate the Efficacy and Safety of SEP-363856 in Acutely Psychotic Subjects with Schizophrenia

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EMERGENCY CONTACTS

Table 1: Emergency Contact Information

Role in Study	Name	Contact Information
Responsible Physician	PPD , MD PPD Head of Global Clinical Research, Psychiatry Sunovion Pharmaceuticals, Inc.	Mobile: PPD Email: PPD
Medical Monitor	PPD MD, Psych, PhD PPD Central Nervous System Medical & Scientific Services Data Sciences, Safety & Regulatory IQVIA	PPD Office: PPD Mobile: PPD Email: PPD
24-Hour Urgent Medical Contact	IQVIA Medical Emergency Contact Center	US: +CCI or CCI Europe: CCI
SAE/Pregnancy Reporting	PPD Pharmacovigilance (PVG)	Hotline Number: CCI Fax (US): CCI Fax (Europe): CCI Email: CCI

1. SYNOPSIS

Name of Sponsor/Company: Sunovion Pharmaceuticals Inc.

Name of Investigational Product: SEP-363856

Title of Study: A Randomized, Double-blind, Parallel-group, Placebo-controlled, Fixed-dose, Multicenter Study to Evaluate the Efficacy and Safety of SEP-363856 in Acutely Psychotic Subjects with Schizophrenia

Proposed Indication: Schizophrenia

Study Centers: Approximately 60 global study centers

Phase of Development: 3

Study Objectives:

Primary Efficacy Objective:

To evaluate the efficacy of fixed doses of SEP-363856 (75 and 100 mg/day) compared with placebo in acutely psychotic adult subjects with schizophrenia as measured by the Positive and Negative Syndrome Scale (PANSS) total score.

Secondary Efficacy Objective:

To evaluate the efficacy of fixed doses of SEP-363856 (75 and 100 mg/day) compared with placebo in acutely psychotic adult subjects with schizophrenia as measured by the Clinical Global Impression-Severity (CGI-S) score.

Other Efficacy Objectives:

- To evaluate the efficacy of fixed doses of SEP-363856 (75 and 100 mg/day) compared with placebo in acutely psychotic adult subjects with schizophrenia as measured by:
  - PANSS subscale scores (positive, negative and general psychopathology).
  - Brief Negative Symptom Scale (BNSS).
  - Montgomery-Asberg Depression Rating Scale (MADRS).
- To assess the effects of SEP-363856 on cognition as measured by the Brief Assessment of Cognition in Schizophrenia (BACS).
- To evaluate the effects of SEP-363856 on functional impairment as measured by the Personal and Social Performance Scale (PSP).
- To evaluate the effects of SEP-363856 on health-related quality of life as measured by the EuroQol-5 Dimensions - 5 Levels (EQ-5D-5L).
- To evaluate the effects of SEP-363856 on functional outcome as measured by the University of California San Diego (UCSD) Performance-based Skills Assessments, Brief Version (UPSA-B).
- To evaluate medication satisfaction as measured by the Medication Satisfaction Questionnaire (MSQ).

Safety Objectives:

- To evaluate the safety and tolerability of SEP-363856 (75 and 100 mg/day) using:
  - physical examinations (PE).

- 12-lead electrocardiograms (ECG).
- vital sign measurements.
- adverse event (AE) reports.
- clinical laboratory tests.
- Columbia – Suicide Severity Rating Scale (C-SSRS).
- Simpson-Angus Scale (SAS).
- Barnes Akathisia Rating Scale (BARS).
- Abnormal Involuntary Movement Scale (AIMS).

- To characterize the subjective effects of SEP-363856 on sleep as measured by the Pittsburgh Sleep Quality Index (PSQI).

CCI [redacted]

Study Design:

This is a multicenter, randomized, double-blind, parallel-group, fixed-dosed study evaluating the efficacy and safety of two doses of SEP-363856 (75 and 100 mg/day) versus placebo over a 6-week Treatment Period in acutely psychotic subjects with schizophrenia. This study is projected to randomize approximately 462 subjects to 3 treatment groups (SEP-363856 75 mg/day, SEP-363856 100 mg/day, or placebo) in a 1:1:1 ratio. CCI [redacted] Treatment assignment will be stratified by country. Study drug will be taken at the same time each evening at bedtime and may be taken with or without food.

The study will consist of 3 periods: Screening/Washout (up to 14 days), Treatment (6 weeks inpatient), and a Follow-up Visit (7 days after last study drug dose for subjects who discontinue prior to the Week 6 visit [Visit 9] or who complete the study but do not enroll in the open-label extension study [SEP361-303]) as shown in Figure 1.

Screening/Washout Period (up to 14 days):

Informed consent will be obtained from each subject before any study procedures are performed. Subjects will be evaluated for eligibility during a screening phase of up to 14 days, during which they will be tapered off all psychotropic medications (except as noted in Section 10.3.4) in a manner that is consistent with labeling recommendations and conventional medical practices.

Subjects may be hospitalized during the screening/washout period at the discretion of the Investigator.

The Screening Period may be extended for up to 7 days after approval from the Medical Monitor.

Subjects who screen fail may be re-screened up to two times, if judged appropriate by the Investigator, after discussion with the Medical Monitor. Re-screened subjects will be re-consented, assigned a new subject number, and all Visit 1 procedures will be repeated.

Double-Blind Treatment Period (6 weeks):

Subjects will be inpatient during the entire double-blind Treatment Period through Week 6/Early Termination (ET). Subjects may be eligible for discharge following the Week 6/ET visit.

Randomization/Treatment: At Baseline (Day 1), subjects who have successfully completed the washout of prior medication and have met the eligibility criteria (see Section 8), will be randomly assigned via an interactive web response system (in a 1:1:1 ratio) to one of three treatment arms: SEP-363856 75 mg/day, SEP-363856 100 mg/day or placebo. Dosing of study drug will begin the evening of the Baseline visit. Treatment will continue once-daily, in the evening at bedtime, for the remainder of the 6-week Treatment Period, during which the procedures outlined in Table 2 will be conducted.

All subjects will receive 50 mg/day or matching placebo for the first three days of the Treatment Period. All subjects will begin receiving 75 mg/day or matching placebo on Day 4. Those subjects assigned to 100 mg/day will begin that dose on Day 8.

All subjects will receive 50 mg/day or matching placebo for the first three days of the Treatment Period. All subjects will begin receiving 75 mg/day or matching placebo on Day 4. Those subjects assigned to 100 mg/day will begin that dose on Day 8. The investigator may request a onetime dose reduction after Day 8 and up to Week 4 (Visit 7) for reasons of safety or tolerability as judged by the Investigator. If the Investigator decides a dose reduction is needed, subjects assigned to the 100 mg/day treatment group will have their dose reduced to 75 mg/day while subjects assigned to 75 mg/day and placebo will remain on their assigned dose (blinded dummy dose reduction for 75 mg/day and placebo). The Investigator and subject will remain blinded to the treatment group assignment and therefore will not know if the dose reduction occurred. Subjects will not be informed that only the 100 mg/day dose group has the possibility of actually receiving a dose reduction. Dose reductions are allowed only once. Subjects unable to tolerate the study medication after a dose reduction (blinded dummy dose reduction or actual dose reduction) will be discontinued from the study. No dose reductions are allowed before Day 8 or after Week 4 (Visit 7). If a dose reduction is required between study visits, a subject will undergo an unscheduled visit for drug dispensation.

Day passes may be granted during the double-blind Treatment Period if the subject is judged by the Investigator to be clinically stable and appropriate for a day pass, and prior approval from the Medical Monitor is obtained. The pass must be limited to a maximum of a half day in duration, and the subject must be accompanied by a staff member. Investigators should follow standard local facility or institutional procedures to ensure subject safety during the time outside of the clinical study center and upon return.

End of Double-Blind Treatment Period:

Subjects will have an End of Treatment (EOT) visit at Week 6 (Visit 9). For subjects who have received study drug and who prematurely discontinue from the study treatment, every effort should be made to complete the final evaluation procedures within 48 hours of the last study drug dose at the early termination (ET) visit.

Subjects who complete the 6-week double-blind Treatment Period will be eligible to participate in a separate open-label extension study (Study SEP361-303) for an additional 52 weeks.

Subjects may be eligible for discharge following the Week 6/ET visit.

Follow-up Period (1 week):

Subjects who discontinue early from the study or complete the study and do not enter the extension study will be required to complete the Follow-up Visit 7 days (± 2 days) post last dose of study drug. For subjects who do not enroll in the extension study, upon completion or early discontinuation from the double-blind treatment phase, hospitalization for up to an additional 7 days during the Follow-up Period for the purpose of stabilizing the subject may be allowed after prior authorization from the Medical Monitor.

If a subject requires continued hospitalizations during the Follow-up Period, a serious adverse event (SAE) should be reported once the hospitalization has lasted more than 7 days after the last dose of study drug, unless the hospitalization was due to social reasons (eg, the subject lacks transportation to living environment or lacks stable living environment).

Number of Subjects (planned): 462 subjects (154 subjects per treatment group) are planned to be randomized. CCI [redacted]. At least 40% of randomized subjects will be female.

Diagnosis and Key Criteria for Subject Inclusion:

Section 8 of the full protocol includes the complete list of inclusion and exclusion criteria.

Key Inclusion criteria (not all inclusive):

- Male or female subject between 18 to 65 years of age (inclusive) at the time of consent.
- Subject meets DSM-5 criteria for schizophrenia as established by clinical interview at Screening (using the DSM-5 as a reference and confirmed using the Structured Clinical Interview for DSM-5, Clinical Trials Version [SCID-CT]).
- Subject must have a CGI-S score ≥ 4 at Screening and Baseline.
- Subject must have a PANSS total score ≥ 80 and a PANSS item score ≥ 4 on 2 or more of the following PANSS items: delusions, conceptual disorganization, hallucinations, and unusual thought content at Screening and Baseline.
- Subject has an acute exacerbation of psychotic symptoms (persisting no longer than 2 months prior to providing informed consent for this study).
- Subject has marked deterioration of functioning in one or more areas, such as occupational, social, or personal care or hygiene.
- Subject has had no more than 3 prior lifetime inpatient hospitalizations for the treatment of an acute psychotic episode or exacerbation of schizophrenia (not including hospitalization at the time of Screening, during Screening or at Baseline). Hospitalization history must be informed by sources other than the subject's own report. This should include medical records and/or documented correspondence with a treating psychiatrist or mental healthcare provider/staff, but can also include information from a reliable informant who is familiar with the subject's psychiatric history (eg, family member, caregiver, case worker, etc.). CCI [redacted]

Key Exclusion criteria (not all inclusive):

- Subject has had a decrease (improvement of symptoms) of ≥ 20% on the PANSS total score between Screening and Baseline.
- Subject has been hospitalized for more than 2 consecutive weeks immediately before screening unless the hospitalization was for reasons unrelated to acute psychotic exacerbation. For example, a subject who is in a long-term hospital setting, is experiencing an acute exacerbation, and is transferred to an acute treatment unit is eligible for the study.
- Subject has a DSM-5 diagnosis or presence of symptoms consistent with a DSM-5 diagnosis other than schizophrenia. Exclusionary disorders include but are not limited to alcohol use disorder (within past 12 months or for a total of ≥ 10 years during the subject's lifetime), substance (other than nicotine or caffeine) use disorder within past 12 months or for a total of

≥ 10 years during the subject's lifetime, major depressive disorder, bipolar I or II disorder, schizoaffective disorder, obsessive compulsive disorder, and posttraumatic stress disorder. Symptoms of mild to moderate mood dysphoria or anxiety are allowed so long as these symptoms are not the primary focus of treatment.

- Subject is judged to be resistant to antipsychotic treatment by the Investigator, based on failure to respond to 2 or more marketed antipsychotic agents within a 1-year period prior to Screening, given at an adequate dose as per labeling, for at least 4 weeks.
- Subject answers "yes" to "Suicidal Ideation" Item 4 (active suicidal ideation with some intent to act, without specific plan) or Item 5 (active suicidal ideation with specific plan and intent) on the C-SSRS assessment at Screening (ie, in the past one month) or Baseline (ie, since last visit).
- Subject is at significant risk of harming self, others, or objects based on Investigator's judgment.
- Subject has attempted suicide within 6 months prior to Screening.
- Subject is involuntarily hospitalized.
- Subject has received a total dose of antipsychotic medication equivalent to ≥ 12.0 mg/day of haloperidol within the current acute psychotic episode. Subject may be eligible if such treatment is less than 2 weeks in duration after consultation with the Medical Monitor.
- Clozapine used at 200 mg/day or less for insomnia, agitation, or anxiety must be discontinued prior to randomization over a 1–2-week period, as judged to be safe by the investigator. Subjects with a history of treatment with clozapine for any reason at doses greater than 200 mg/day or at doses less than or equal to 200 mg/day for a usage other than insomnia, agitation, or anxiety are excluded from study participation.
- Subject has received electroconvulsive therapy treatment within the 3 months prior to Screening or is expected to require electroconvulsive therapy (ECT) during the study.
- Subject has any clinically significant unstable medical condition or any clinically significant chronic disease that in the opinion of the Investigator, would limit the subject's ability to complete and/or participate in the study.
- Subject has received an investigational drug product or device within 90 days prior to signing informed consent or has participated in more than 3 studies in psychiatric indications of investigational drug products or devices within their lifetime.
- Subject has previously received SEP-363856 or was previously enrolled in a SEP-363856 clinical study.

Investigational Product, Dosage and Mode of Administration:

SEP-363856 will be supplied as matching 50 mg, 75 mg, or 100 mg tablets. SEP-363856 will be taken orally once a day (QD) at the same time each evening at bedtime and may be taken with or without food.

Subjects randomized to SEP-363856 will receive SEP-363856 throughout the study according to the schedule defined in the Study Design in Section 7.1.

Duration of Treatment: 6 weeks

Reference Therapy, Dosage and Mode of Administration:

Placebo treatment will be provided as matching placebo tablets. Placebo will be taken orally QD at the same time each evening at bedtime and may be taken with or without food.

Subjects randomized to placebo will receive matching placebo tablets throughout the study.

Concomitant Medications:

Prior Medications:

Treatment with oral psychotropic medications and any other medications with a propensity for psychotropic effects (with the exception of the medications described in Section 10.3.4) must be discontinued at least 3 days or 5 half-lives (whichever is longer) prior to randomization in a manner that is consistent with conventional medical practice. The following medications have additional washout requirements as specified below:

- Monoamine oxidase inhibitors (MAOIs) must be discontinued at least 28 days prior to randomization.
- Fluoxetine or fluoxetine/olanzapine combination must be discontinued at least 28 days prior to randomization.
- Clozapine used at 200 mg/day or less for insomnia, agitation, or anxiety must be discontinued prior to randomization over a 1 to 2-week period, as judged to be safe by the investigator. Subjects with a history of treatment with clozapine for any reason at doses greater than 200 mg/day or at doses less than or equal to 200 mg/day for an indication other than insomnia, agitation, or anxiety are excluded from study participation.
- Depot neuroleptics must have been discontinued at least one treatment cycle or at least 30 days (whichever is longer) prior to the randomization visit.

Treatment with sedative hypnotics is permitted during the screening period but should be tapered as clinically appropriate to conform with and adequately prepare the subject for the protocol-specified limitations applicable to these agents following randomization (see Section 10.3.4). Subjects should not be taken off current effective medications for treatment of schizophrenia for purposes of participating in this study.

Treatment with medications used to treat movement disorders must be discontinued at least 1 day prior to randomization.

Prohibited Medications:

Psychotropic medications and medications with a propensity for psychotropic effects are not permitted during the 6-week Treatment Period up through the End of Treatment (EOT) Visit , except for the medications discussed in Section 10.3.4.

The use of herbal supplements, dietary supplements or other complementary or alternative medications for treating psychiatric indications are not permitted during the double-blind Treatment Period up through the EOT Visit.

Use of psychotropic medications, herbal/dietary supplements, or other complementary/ alternative medications for treating psychiatric indications after the last dose of study medication is permitted for those not continuing into the extension study (SEP361-303) provided they are not administered prior to the final PANSS assessment. Subjects who are administered a psychotropic medication (other than the study drug and the acceptable medications described in Section 10.3.4) for the purposes of treating an exacerbation of symptoms associated schizophrenia or due to lack of efficacy of the study treatment will be discontinued from the study.

Allowed Concomitant Psychotropic Medications:

Treatment with benztropine (benzotropine outside the United States [US]) up to 6 mg/day is permitted, as needed, for movement disorders. In cases where benztropine is not available or a subject has had an inadequate response or intolerability to benztropine treatment, the following medications may be used to treat acute extrapyramidal symptoms (EPS): biperiden (up to 16 mg/day) or trihexyphenidyl (up to 15 mg/day) or diphenhydramine (up to 100 mg/day). Treatment with propranolol (up to 120 mg/day) is permitted as needed for akathisia. These allowed medications for the treatment of EPS and akathisia may be given in any formulation (oral, IM or IV) as deemed appropriate by the Investigator. Medications used to treat movement disorders should not be given prophylactically. They are to be tapered and discontinued 1 day prior to randomization but may be reinstated if symptoms emerge post-randomization during the study.

Concomitant use of lorazepam, temazepam, eszopiclone, zaleplon, zolpidem and zolpidem CR is permitted at the discretion of the Investigator with the following restrictions:

- Oral lorazepam (or equivalent benzodiazepine) is permitted for clinically significant anxiety/agitation or as a sedative/hypnotic up to a maximum daily dose of 6 mg/day. Intramuscular lorazepam is permitted up to 4 mg/day for acute anxiety/agitation, as clinically indicated. Lorazepam should be used sparingly, when clinically required, per Investigator judgment.
- Temazepam (≤ 30 mg/day), eszopiclone (≤ 3 mg/day), zopiclone (≤ 7.5 mg/day), zaleplon (≤ 20 mg/day), zolpidem (≤ 10 mg/day), and zolpidem CR (≤ 12.5 mg/day) may be administered at bedtime for insomnia, as needed.
- Medications that are used for insomnia should be administered no more than once nightly and should not be used in combination.
- Medications used for the treatment of anxiety/agitation and insomnia (eg, lorazepam and zolpidem) should not be used in close temporal proximity (defined as administration within 2 hours of each other).

In regions that do not have the above specified drugs available, similar drugs at equivalent dosages will be permitted in consultation with the Medical Monitor.

The date and time of the last dose of any concomitant psychotropic medication(s) taken prior to scheduled efficacy assessments must be recorded at each visit. Subjects should be encouraged to avoid taking any psychotropic medication (or any agents that my cause sedation) within 8 hours of efficacy assessments.

Opioids for the treatment of pain may be allowed in rare cases for a limited period of time with prior authorization from the Medical Monitor.

Concomitant Non-psychotropic Medications:

Non-psychotropic medications used to treat mild, chronic medical conditions may be used during screening and after randomization if the dose and regimen have been stable (± 25% total daily dose) for at least 30 days prior to Screening. The dose for the concomitant medication may change, as needed, after randomization (or be discontinued). This includes β-adrenergic antagonists used to treat stable hypertension. Routine vaccines (ie, seasonal influenza, pneumonia, etc.) are allowed based on the Investigator's judgment. Female subjects may use Female subjects may use contraception as detailed in Section 10.5.

Use of non-prescription pain medications (eg, aspirin, acetaminophen/paracetamol) are allowed during all phases of the study provided these medications do not have a propensity for psychotropic effects.

The Medical Monitor should be consulted, if possible, before administering medications for short-term treatment of an acute medical condition. If medications are administered for short-term treatment of an acute medical condition without prior consultation with the Medical Monitor and the appropriateness for the subject to continue in the study should be discussed with the Medical Monitor.

See Section 10.3 of full protocol for further information.

Study Endpoints:

Primary Endpoint:

Change from Baseline in PANSS total score at Endpoint (Week 6).

Secondary Efficacy Endpoint:

Change from Baseline in CGI-S score at Endpoint (Week 6).

Other Efficacy Endpoints:

- At each scheduled visit except Endpoint (Week 6), change from Baseline in
  - PANSS total score.
  - CGI-S score.
- At each scheduled visit, change from Baseline in
  - PANSS subscale scores.
  - BNSS total score.
  - MADRS total score.
  - BACS composite score.
  - PSP total score.
  - EQ-5D-5L: visual analog scale (VAS), index score and dimension score.
  - UPSA-B total score.
  - MSQ score.
- PANSS response, defined as a 20% or greater improvement from Baseline in PANSS total score at each scheduled visit.
- Tobacco use at Baseline and Endpoint.

Safety Endpoints:

- The incidence of overall AEs, serious AEs (SAEs), and AEs (or SAEs) leading to discontinuation.
- Observed values and changes from Baseline at each scheduled visit in clinical laboratory tests (hematology, chemistry, and urinalysis), vital signs (including temperature, body weight, body mass index (BMI), waist circumference, blood pressure [supine and standing], pulse rate [supine and standing] and respiration rate) and 12-lead ECG parameters.
- Frequency and severity of suicidal ideation and suicidal behavior based on the C-SSRS.
- Change from Baseline in SAS, BARS and AIMS scores at each scheduled visit.
- Change from Baseline in PSQI global score at each scheduled visit.

CCI [redacted]

Statistical Methods:

General Methodology

The efficacy analyses will be based on the modified Intent-to-Treat (mITT) population, which includes all subjects who are randomized, have received at least one dose of study drug, and have a Baseline and at least one post-Baseline efficacy measurement in PANSS or CGI-S. The safety assessments will use the Safety population, which includes all subjects who are randomized and have received at least one dose of study drug.

Analysis of Primary Efficacy Endpoint

The primary efficacy estimand is defined as the difference between each SEP-363856 dose level and placebo in the mean change of PANSS total score from Baseline to Week 6 in acutely psychotic adult subjects with schizophrenia as characterized by the study inclusion/exclusion criteria, in the hypothetical setting where the subjects were able to stay on study and remain on the study treatment for 6 weeks.

For the primary analysis of the primary efficacy endpoint, data will be analyzed using a mixed model for repeated measures (MMRM) under the missing-at-random (MAR) assumption. Under this assumption, the efficacy outcome of subjects in each treatment group after early discontinuation will exhibit the same future evolution as subjects in the same group remaining in the study. The MMRM model will include fixed factors for treatment, visit (Day 4, Weeks 1, 2, 3, 4, 5 and 6; as a categorical variable), country, and treatment-by-visit interaction, and include Baseline PANSS total score as a covariate. An unstructured covariance matrix will be used to model the within-subject correlation. Kenward-Roger approximation will be used to calculate the denominator degrees of freedom. The main estimator of the primary efficacy estimand is the least squares (LS) mean difference in PANSS total score change from Baseline at Week 6 from the primary analysis model of observed repeated measures data.

Sensitivity analyses will be conducted to assess the impact of missing data on the primary analysis result by deviating away from the MAR assumption. The methods will include a tipping point analysis, a copy reference analysis, and a jump to reference analysis.

Analysis of Secondary Efficacy Endpoint

The secondary efficacy endpoint of change from Baseline in CGI-S score at Endpoint (Week 6) will be analyzed using the same methodology as the primary efficacy endpoint.

Multiplicity Adjustment

Type I error control will only be performed for the primary analysis of the primary and secondary efficacy endpoints in the mITT population. Nominal p-values will be reported for all other statistical tests.

Multiplicity adjustment will be applied to address three sources of multiplicity in this trial: (1) analysis of the primary endpoint and the secondary efficacy endpoint; (2) analysis of two dose-placebo comparisons CCI [redacted] The first two sources of multiplicity will be addressed through a Hochberg-based gatekeeping procedure derived using the enhanced mixture method. The null hypotheses of no difference in treatment effect between each of the SEP-363856 dose levels and placebo associated with the primary and the secondary efficacy endpoint will be grouped into two hierarchical families: Family F1 includes the primary endpoint hypotheses, and Family F2 includes the secondary efficacy endpoint hypotheses. The truncated Hochberg ($\gamma = 0.9$) procedure will be applied to the hypotheses in Family F1 (H1 and H2) and the regular Hochberg procedure will be applied to the hypotheses in Family F2 (H3 and H4). There is a serial logical restriction among the hypotheses: H3 is testable only if H1 is rejected; H4 is testable only if H2 is rejected.

CCI [redacted]

Analysis of Other Efficacy Endpoints

The efficacy endpoints of PANSS total score and CGI-S score change from Baseline at scheduled visits other than the Endpoint (Week 6) will be analyzed as part of the MMRM models described above for the primary endpoint and secondary efficacy endpoint. Efficacy endpoints related to PANSS subscales, BNSS, and MADRS will be analyzed using a MMRM model similar to the primary analysis model of the primary efficacy endpoint. Continuous efficacy endpoints related to BACS, PSP, UPSA-B, EQ-5D-5L, and MSQ outcome measures will be analyzed by an analysis of covariance (ANCOVA) model which includes factors for treatment and country, and the respective Baseline score as the covariate.

Proportion of subjects who achieve PANSS response at each scheduled visit will be calculated, and missing PANSS total score at Endpoint (Week 6) will be imputed using the last-observation-carried-forward (LOCF) method to derive PANSS response at the Week 6 LOCF endpoint. A logistic regression analysis will be performed with the responder indicator as the dependent variable, treatment and geographic region as fixed factors, and Baseline PANSS total score as a covariate.

Analysis of Safety Endpoints

Safety data including AEs, laboratory values, vital signs, ECG measurements, and C-SSRS, will be summarized by treatment.

Adverse events, AEs leading to discontinuation, and serious AEs will be summarized by presenting, for each treatment group, the number and percentage of subjects with any AEs, and AEs by system organ class and preferred term. Adverse events will be further summarized by severity and by relationship to study drug.

Sample Size: A total of 369 subjects (123 per treatment group: SEP-363856 75 mg/day, SEP-363856 100 mg/day, and placebo) with a global 2-sided alpha of 0.05 will provide 90% power to reject the null hypothesis of no difference in the mean primary endpoint against placebo for at least one SEP-363856 dose level and 75% power to reject the null hypothesis for both SEP-363856 dose levels using a truncated Hochberg ($\gamma = 0.9$) procedure, assuming a treatment effect size of 0.385 for both dose levels. A clinically meaningful effect size of 0.385 was estimated based on results from Study SEP361-201 and review of published studies of other antipsychotics for the short-term treatment of schizophrenia. The observed effect size in Study SEP361-201 was 0.45 after four weeks of flexible dosing with SEP-363856 at 50 or 75 mg/day. An upward adjustment of approximately 25% is used to compensate for information lost due to subjects who are randomized but drop out and are without complete efficacy data at all scheduled visits. The total sample size will be 462 subjects randomized in 1:1:1 allocation ratio (or 154 subjects per treatment group). CCI [redacted]

Table 2: Schedule of Assessments

	Inpatient or Outpatient	Inpatient								Inpatient or Outpatient
Study Visit Number **Study Visit Week**	**Visit 1 Screening[a]**	**Visit 2 Baseline**	**Visit 3 Day 4**	**Visit 4 Week 1**	**Visit 5 Week 2**	**Visit 6 Week 3**	**Visit 7 Week 4**	**Visit 8 Week 5**	**Visit 9 Week 6[b] EOT or ET[c]**	**Visit 10 Week 7[d] Follow-up**
Study Visit Day	**-14 to -1**	**1**	**4**	**8 ± 1 day**	**15 ± 1 day**	**22 ± 1 day**	**29 ± 1 day**	**36 ± 1 day**	**43 ± 1 day**	**7 ± 2 days after last dose**
Obtain informed consent	X									
CCI										
Review inclusion/exclusion criteria	X	X								
Prior/concomitant medication review	X	X	X	X	X	X	X	X	X	X
Randomize (IWRS) to treatment		X								
Dispensation of study drug[e]		X		X	X	X	X	X		
Study drug accountability				X	X	X	X	X	X	
Demography	X									
Medical history	X									
Psychiatric history	X									
Tobacco use information	X								X	
SCID-CT[f]	X									
Physical and neurological examination	X								X	X
Height	X									
Vital signs[g]	X	X	X	X	X	X	X	X	X	X
Weight (including BMI)[h]	X	X				X			X	

Table 2: Schedule of Assessments (Continued)

	Inpatient or Outpatient	Inpatient								Inpatient or Outpatient
Study Visit Number **Study Visit Week**	**Visit 1 Screening[a]**	**Visit 2 Baseline**	**Visit 3 Day 4**	**Visit 4 Week 1**	**Visit 5 Week 2**	**Visit 6 Week 3**	**Visit 7 Week 4**	**Visit 8 Week 5**	**Visit 9 Week 6[b] EOT or ET[c]**	**Visit 10 Week 7[d] Follow-up**
Study Visit Day	**-14 to -1**	**1**	**4**	**8 ± 1 day**	**15 ± 1 day**	**22 ± 1 day**	**29 ± 1 day**	**36 ± 1 day**	**43 ± 1 day**	**7 ± 2 days after last dose**
Waist circumference		X				X			X	
12-lead Electrocardiogram (ECG)	X	X		X					X	
Hematology, chemistry, and urinalysis[i]	X	X							X	
Blood sample for hepatitis Screening	X									
Serum follicle stimulating hormone (FSH)[j]	X									
Serum human chorionic gonadotropin (β-hCG), (females)	X									
CCI [redacted]										
Urine drug screen[m]	X	X							X	
Urine β-hCG (females)[n]		X							X	X
Positive and Negative Syndrome Scale (PANSS)	X	X	X	X	X	X	X	X	X	
Clinical Global Impression – Severity (CGI-S)	X	X	X	X	X	X	X	X	X	
Brief Negative Symptom Scale (BNSS)		X	X	X	X	X	X	X	X	

Table 2: Schedule of Assessments (Continued)

	Inpatient or Outpatient	Inpatient								Inpatient or Outpatient
Study Visit Number **Study Visit Week**	**Visit 1 Screening[a]**	**Visit 2 Baseline**	**Visit 3 Day 4**	**Visit 4 Week 1**	**Visit 5 Week 2**	**Visit 6 Week 3**	**Visit 7 Week 4**	**Visit 8 Week 5**	**Visit 9 Week 6[b] EOT or ET[c]**	**Visit 10 Week 7[d] Follow-up**
Study Visit Day	**-14 to -1**	**1**	**4**	**8 ± 1 day**	**15 ± 1 day**	**22 ± 1 day**	**29 ± 1 day**	**36 ± 1 day**	**43 ± 1 day**	**7 ± 2 days after last dose**
Montgomery-Asberg Depression Rating Scale (MADRS)		X	X	X	X	X	X	X	X	
Columbia Suicide Severity Rating Scale (C-SSRS)	X	X	X	X	X	X	X	X	X	X
Simpson-Angus Scale (SAS)[o]		X							X	
Barnes Akathisia Rating Scale (BARS)[o]		X							X	
Abnormal Involuntary Movement Scale (AIMS)[o]		X							X	
Pittsburg Sleep Quality Index (PSQI)		X							X	
Brief Assessment of Cognition in Schizophrenia (BACS)		X							X	
University of California San Diego (USCD) Performance-based Skills Assessment, Brief Version (UPSA-B)		X							X	
Personal and Social Performance Scale (PSP)		X							X	
EuroQol – 5 Dimensions – 5 Levels (EQ-5D-5L)		X							X	
Medication Satisfaction Questionnaire (MSQ)	X[p]								X	

Table 2: Schedule of Assessments (Continued)

	Inpatient or Outpatient	Inpatient								Inpatient or Outpatient
Study Visit Number Study Visit Week	Visit 1 Screening[a]	Visit 2 Baseline	Visit 3 Day 4	Visit 4 Week 1	Visit 5 Week 2	Visit 6 Week 3	Visit 7 Week 4	Visit 8 Week 5	Visit 9 Week 6[b] EOT or ET[c]	Visit 10 Week 7[d] Follow-up
Study Visit Day	-14 to -1	1	4	8 ± 1 day	15 ± 1 day	22 ± 1 day	29 ± 1 day	36 ± 1 day	43 ± 1 day	7 ± 2 days after last dose
Healthcare resource utilization		X								
Pretreatment/Adverse events (AE) monitoring[q]	X	X	X	X	X	X	X	X	X	X
Duplicate Subject Check[r]	X								X	

Abbreviations: AE = adverse event; β-hCG = human chorionic gonadotropin; BMI = Body Mass Index; BNNS = Brief Negative Symptom Scale; EOT = end of treatment; ET = early termination; IWRS = interactive web response system; SCID-CT = Structured Clinical Interview for DSM-5, Clinical Trials Version; UPSA-B = University of California San Diego (UCSD) Performance-based Skills Assessment.

[a] Subjects who screen fail may be re-screened up to two times after consultation with the Medical Monitor. Screening assessments may occur over multiple days. Hospitalization during Screening is optional at the Investigator's discretion. The Screening Period may be extended for up to 7 days after approval from the Medical Monitor.

[b] All procedures and assessments scheduled for Week 6 will be utilized as Baseline procedures and assessments for the open-label extension study (SEP361-303).

[c] If a subject discontinues from the study, all Early Termination (ET) procedures should be performed at the ET visit, within 48 hours of last study dose.

[d] Subjects who discontinue early from the study or complete the study and do not enter the extension study (SEP361-303) will have a safety Follow-up Visit (7 [± 2]) days after their last dose of study drug. Upon completion or early discontinuation from the study, hospitalization will be allowed for up to an additional 7 days to stabilize the subject, if necessary. Prior authorization for the hospitalization must be provided by the Medical Monitor.

[e] All study drug will be taken once daily in the evening at bedtime by mouth, with or without food.

[f] The SCID-CT will be used to support the DSM-5 diagnosis and must be administered by a qualified rater listed on Form 1572 with at least 2 years' experience with the population under study.

[g] Vital signs will include respiratory rate, oral body temperature and supine and standing measurements of blood pressure and pulse rate.

[h] BMI will be calculated and recorded in the electronic case report form (eCRF) at the clinical site at screening. For other visits, BMI will be calculated in the eCRF and during statistical analysis.

[i] Subjects must be fasted (no food or drink except water at least 8 hours prior to specified blood tests). Blood samples should be drawn in the morning followed by a snack or meal. Serum prolactin results will be blinded after the Screening visit. A list of clinical laboratory tests is provided in Section 22.

[j] Blood samples for follicle stimulating hormone (FSH) will be collected for post-menopausal women or if menopause is suspected.

[k] Requested, but not required for participation in the study.

[l] CCI [redacted]

[m] If a subject is issued a day pass, an unscheduled urine drug screen will be performed upon returning to the site. Urine drug screen may be ordered at other visits as deemed clinically appropriate. Positive results should be discussed with the Medical Monitor.

[n] Any positive urine β-hCG test should be confirmed by a serum β-hCG test.

[o] Unscheduled SAS, BARS and AIMS scales should be administered if a subject develops extrapyramidal symptoms (EPS) requiring treatment.

[p] Only those subjects who were currently treated with an antipsychotic medication or had been treated with antipsychotic medications within 30 days of the Screening Visit will be analyzed.

[q] Events occurring prior to first dose of study drug are programmatically identified as pretreatment events. Events occurring after first dose of study drug are programmatically identified as adverse events.

[r] Signed consent collected at screening to perform the Duplicate Subject Check (US only). Following the last contact with a subject, the duplicate enrollment system should be updated, as appropriate (US sites only).

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2. TABLE OF CONTENTS

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LIST OF TABLES

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3. LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

The abbreviations and the definition of key study terms used in the clinical study protocol are shown in Table 3 and Table 4.

Table 3: List of Abbreviations

Abbreviation	Full Form
AE	Adverse event
AIMS	Abnormal Involuntary Movement Scale
ALT	Alanine aminotransferase
ANCOVA	Analysis of covariance
AST	Aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical
BACS	Brief Assessment of Cognition in Schizophrenia
BARS	Barnes Akathisia Rating Scale
BMI	Body mass index
BNSS	Brief Negative Symptom Scale
BUN	Blood urea nitrogen
CFR	Code of Federal Regulations
CGI-S	Clinical global impression - severity
CLIA	Clinical Laboratory Improvement Amendments
CNS	Central nervous system
CR	Controlled release
CRF	Case report form
CRO	Contract research organization
CS	Clinically significant
C-SSRS	Columbia – Suicide Severity Rating Scale
CCI	[redacted]
DSMB	Data safety monitoring board
ECG	Electrocardiogram
ECT	Electroconvulsive therapy
EDC	Electronic data capture
EOT	End of Treatment
EPS	Extrapyramidal symptoms
EQ-5D-5L	EuroQol– 5 Dimensions – 5 Levels

Table 3: List of Abbreviations (Continued)

Abbreviation	Full Form
ET	Early termination
FDA	U.S. Food and Drug Administration
fMRI	functional magnetic resonance imaging (fMRI)
GCP	Good Clinical Practice
5-HT	5-hydroxytryptamine (serotonin)
HIV	Human immunodeficiency virus
ICF	Informed consent form
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
IM	Intramuscular
IND	Investigational New Drug
IPD	Important protocol deviation
IRB	Institutional Review Board
CCI	
IV	Intravenous
IWRS	Interactive web response system
LOCF	Last Observation Carried Forward
LIMS	Laboratory information management system
LS	Least squares
MADRS	Montgomery-Asberg Depression Rating Scale
MAOIs	Monoamine oxidase inhibitors
MAR	Missing-at-random
MedDRA	Medical Dictionary for Regulatory Activities
mITT	Modified Intention-to-Treat
MMRM	Mixed-effects Models Repeated Measures
MSQ	Medication Satisfaction Questionnaire
MTD	Maximum tolerated dose
NCE	New chemical entity
NCS	Not clinically significant
PANSS	Positive and negative syndrome scale
PD	Pharmacodynamic(s)

Table 3: List of Abbreviations (Continued)

Abbreviation	Full Form
PE	Physical examination
CCI	[redacted]
PR	Time between P wave and QRS in electrocardiography
PSP	Personal and Social Performance Scale
PSQI	Pittsburgh Sleep Quality Index
PT	Preferred term
PVG	Pharmacovigilance
QD	Once daily
QRS	Electrocardiographic wave (complex or interval)
QT interval	Electrocardiographic interval from the beginning of the QRS complex to the end of the T wave
QTc	QT interval corrected for heart rate
REM	Rapid eye movement
RR interval	Distance between two consecutive R waves
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SAS	Simpson-Angus Scale
SCID-CT	Structured Clinical Interview for DSM-5, Clinical Trials Version
SOC	System organ class
TAAR1	trace amine associated 1 receptors
UCSD	University of California San Diego
UDS	Urine drug screen
US, USA	United States, United States of America
UPSA-B	University of California San Diego Performance-based Skills Assessment, Brief Version
VAS	Visual analogue scale
WBC	White blood cells
WHO-DD	World Health Organization - Drug Dictionary

Table 4: Definition of Key Study Terms

Terms	Definition of terms
CRF	A printed, optical, or electronic document designed to record all of the protocol required information to report to the Sponsor for each study subject.
Screened Subject	Any subject who signed the study specific informed consent and completed at least one study related procedure.
Screen Failures	Any subject who signed the study specific informed consent but either failed to meet study requirements during screening or met study requirements at screening but was not randomized.
Study Drug (or Study medication)	Term to cover investigational drug and placebo.
Treatment Period	The period of the study in which the study drug is administered.
Randomized Subject	Any subject who was randomized into the Treatment Period of the study and was assigned a randomization number.
Completed Subject	Any subject who participated throughout the duration of the Treatment Period, up to and including Visit 9 with a minimum of the Positive and Negative Syndrome Scale (PANSS) assessment completed at Visit 9.
Early Termination Subject	Any subject who was successfully screened and randomized into the Treatment Period of the study but did not complete the Treatment Period of the study.
End of Treatment	The day that the subject receives protocol-defined last dose of the study drug.

4. INTRODUCTION

4.1. Background

Schizophrenia is a chronic and disabling neuropsychiatric disorder characterized by a mixture of positive symptoms (eg, hallucinations, delusions, and thought and movement disorders), negative symptoms (eg, flat affect, anhedonia, alogia, and avolition), and cognitive deficits (eg, impaired memory, attention, and planning/organizing). Mood symptoms such as depression, anxiety, hostility, and excitement can also be present in patients with schizophrenia (Patel-2007; NIMH-2010). Despite scientific advances, schizophrenia remains one of the most challenging diseases to treat due to its variable nature, the heterogeneity of clinical response, the side effects of treatment, and its association with high morbidity and mortality (Lehman-2004; Tandon-2008; NIMH-2010).

Schizophrenia has an estimated population prevalence of approximately 1% (estimated 2.4 million adults) (Narrow-2002; Wu-2006). It affects both genders equally (NIMH-2010), typically first manifesting in young adults, with the peak ages of onset in the early to mid 20s in men and late 20s in women (APA-2000). It is believed to be caused by a combination of genetic and environmental factors (Minzenberg-2008). Dopaminergic, serotonergic and glutamatergic systems are believed to play a role in schizophrenia (Kuroki-2008; Kim-2009).

The current standard of care for the treatment of schizophrenia is the use of second generation antipsychotics or "atypical antipsychotics" (Lehman-2004; Kreyenbuhl-2009; NIMH-2010; Meltzer-2011; Nakamura-2009). These "atypicals" are thought to have fewer extrapyramidal side effects compared to first generation antipsychotics or "typical antipsychotics" (eg, haloperidol) (Leucht-2009; Naber-2009). However, some patients respond poorly to both atypical and typical antipsychotics and some continue to have symptoms and substantial functional/cognitive impairment (Keefe-2006; Webber-2008). Very few patients return to baseline (pre-psychosis) function (Schultz-1999; Pearlson-2000; Kapur-2001). In addition, atypical agents are associated with a variety of other side effects, including weight gain, metabolic syndrome, sedation, QTc prolongation, extrapyramidal symptoms and tardive dyskinesia (Davis-2004; Lieberman-2005; Newcomer-2007; Leucht-2009), which may lead to significant medical problems (cardiovascular disease, diabetes) as well as contribute to poor compliance and treatment discontinuation. The large-scale NIMH-CATIE schizophrenia study found that 70% to 80% of outpatients discontinue medications before 18 months because of lack of efficacy or occurrence of side effects (Lieberman-2005). Noncompliance often leads to relapse of symptoms and the need for rehospitalization (Ascher-Svanum-2010; Munro-2011; Morken-2008). Clearly, an unmet need exists for new, effective, and well-tolerated treatments for schizophrenia.

4.2. Study Conduct Rationale

SEP-363856 is a central nervous system (CNS)-active compound, which shows broad efficacy in animal models of schizophrenia (positive and negative symptoms), cognition and depression. The molecular target responsible for the therapeutic profile of SEP-363856 has not been completely elucidated but may include actions at 5-HT1A and trace amine associated 1 (TAAR1) receptors. Rat electroencephalogram (EEG) studies showed that SEP-363856 suppressed rapid eye movement (REM) sleep in a dose dependent manner. In nonhuman primate

functional magnetic resonance imaging (fMRI) experiments, similar to risperidone, pretreatment with SEP-363856 also reduced the ketamine brain fMRI response in rhesus monkey supporting an antipsychotic-like profile.

As of 24 September 2018, a total of 246 subjects have received oral doses of SEP-363856 in 8 completed Phase 1 studies (SEP361-101, SEP361-103, SEP361-104, SEP361-105, SEP361-106, SEP361-108, SEP361-111 and DA801002). An additional 199 subjects received oral doses of SEP-363856 in studies in adults with schizophrenia (Study SEP361-201 and Study SEP361-202) and 24 subjects in a Phase 1 study (Study DA801004) in Japanese adults with schizophrenia.

Study SEP361-105 was a randomized, single-blind, placebo-controlled, ascending single oral dose study assessing the safety, tolerability, and pharmacokinetic (PK) of SEP-363856 in male and female adults with schizophrenia. This study established the maximum tolerated dose (MTD) of single doses of SEP-363856 in subjects with schizophrenia as 100 mg.

Study SEP361-106 was a 2-part, randomized, single-blind, placebo-controlled, ascending multiple oral dose and open label study assessing the safety, tolerability, and PK profile of SEP-363856 in male and female adults with schizophrenia. Part 1 established the MTD for 7 days of multiple dosing of SEP-363856 without titration as 75 mg/day. In Part 2, treatment with SEP-363856 75 mg/day for 28 days demonstrated improvement in efficacy measures (Positive and negative syndrome scale [PANSS] total score, Clinical Global Impression-Severity [CGI-S]) compared with baseline. Results from this study demonstrated an acceptable safety and tolerability profile of SEP-363856 75 mg/day for up to 28 days in adults with schizophrenia.

Study SEP361-201 was a 4-week, randomized, double-blind, placebo-controlled, multicenter study evaluating the efficacy and safety of SEP-363856 (flexibly-dosed at 50 to 75 mg/day) in acutely psychotic adults with schizophrenia. SEP-363856 demonstrated statistically significant improvement in the PANSS total score compared to placebo at Week 4 (primary endpoint) with an effect size of 0.45. Significant differences favoring the SEP-363856 group were also demonstrated on all secondary efficacy endpoints, including the Clinical Global Impression – Severity scale (CGI-S), PANSS subscales encompassing positive, negative and general psychopathology symptoms, the Montgomery-Asberg Depression Rating Scale (MADRS) and Brief Negative Symptom Scale (BNSS). Overall, the safety and tolerability profile were comparable to placebo. There were no clinically relevant findings related to electrocardiogram (ECG) parameters, laboratory parameters, vital signs, motor symptoms or suicidality.

Study SEP361-202 is a long-term, open-label extension study to Study SEP361-201, which is evaluating the safety and tolerability of flexibly dosed SEP-363856 (25 to 75 mg/day) in adults with schizophrenia for up to 26 weeks.

Together, these data support continued development of SEP-363856 as a potential treatment for patients with schizophrenia.

The present study is designed to evaluate the efficacy and safety of SEP-363856 at two fixed doses (75 and 100 mg/day) in subjects with an acute exacerbation of schizophrenia. Subjects will be randomized to receive SEP-363856 (75 or 100 mg/day) or placebo for 6 weeks. Titration to the 75 and 100 mg doses is included to improve tolerability.

4.3. Risk-Benefit Assessment

Schizophrenia is a lifelong disorder and despite advances in drug treatment many patients continue to experience significant symptoms, disabling side effects and impaired functioning and quality of life. SEP-363856 has a novel mechanism of action not related to direct antagonism of the D2 receptor.

In an adequate and well-controlled four-week Phase 2 study in adults with schizophrenia (Study SEP361-201), SEP-363856 demonstrated a statistically significant improvement in Positive and Negative Syndrome Scale (PANSS) total score compared to placebo with an effect size of 0.45, supporting antipsychotic efficacy.

Overall, SEP-363856 was well-tolerated in clinical studies to date. The maximum tolerated dose for multiple doses of SEP-363856 in adults with schizophrenia was previously determined to be 75 mg/day in a completed Phase 1 study; however, in the Phase 2 Study SEP361-201, where the majority of subjects received 75 mg/day for 4 weeks, the tolerability and safety profile was shown to be similar to that of placebo. This indicates that a dose higher than 75 mg/day may be tested to maximize efficacy, based on an acceptable expected benefit/risk ratio.

This supports evaluation of SEP-363856 75 to 100 mg/day in adults with schizophrenia in this study.

4.4. Hypothesis

Treatment with SEP-363856 in adult subjects with schizophrenia will result in significantly greater reduction (ie, improvement) in PANSS total score and CGI-S score at Week 6 from Baseline when compared to placebo. The hypotheses of this study are arranged into two hierarchical families. The first family includes hypotheses about the testing of change from Baseline in PANSS total score at Week 6 between each of the SEP-363856 dose levels vs. placebo. The second family of hypotheses are about the testing of change from Baseline in CGI-S score at Week 6 between each of the SEP-363856 dose levels vs. placebo.

5. STUDY OBJECTIVES

5.1. Primary Objective

To evaluate the efficacy of fixed doses of SEP-363856 (75 and 100 mg/day) compared with placebo in acutely psychotic adult subjects with schizophrenia as measured by the Positive and Negative Syndrome Scale (PANSS) total score.

5.2. Secondary Efficacy Objective

To evaluate the efficacy of fixed doses of SEP-363856 (75 and 100 mg/day) compared with placebo in acutely psychotic adult subjects with schizophrenia as measured by the Clinical Global Impression-Severity (CGI-S) score.

5.3. Other Efficacy Objectives

- To evaluate the efficacy of fixed doses of SEP-363856 (75 and 100 mg/day) compared with placebo in acutely psychotic adult subjects with schizophrenia as measured by:
  - PANSS subscale scores (positive, negative and general psychopathology).
  - Brief Negative Symptom Scale (BNSS).
  - Montgomery-Asberg Depression Rating Scale (MADRS).
- To assess the effects of SEP-363856 on cognition as measured by the Brief Assessment of Cognition in Schizophrenia (BACS).
- To evaluate the effects of SEP-363856 on functional impairment as measured by the Personal and Social Performance Scale (PSP).
- To evaluate the effects of SEP-363856 on health-related quality of life as measured by the EuroQol – 5 Dimensions – 5 Levels (EQ-5D-5L).
- To evaluate the effects of SEP-363856 on functional outcome as measured by the University of California San Diego (UCSD) Performance-based Skills Assessments, Brief Version (UPSA-B).
- To evaluate medication satisfaction as measured by the Medication Satisfaction Questionnaire (MSQ).

5.4. Safety Objectives

- To evaluate the safety and tolerability of SEP-363856 (75 and 100 mg/day) using:
  - physical examinations (PE).
  - 12-lead electrocardiograms (ECG).
  - vital sign measurements.
  - adverse event (AE) reports.
  - clinical laboratory tests.

  - Columbia – Suicide Severity Rating Scale (C-SSRS).
  - Simpson-Angus Scale (SAS).
  - Barnes Akathisia Rating Scale (BARS).
  - Abnormal Involuntary Movement Scale (AIMS).
- To characterize the subjective effects of SEP-363856 on sleep as measured by the Pittsburgh Sleep Quality Index (PSQI).

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6. STUDY ENDPOINTS

6.1. Primary Endpoint

Change from Baseline in PANSS total score at Endpoint (Week 6).

6.2. Secondary Efficacy Endpoint

Change from Baseline in CGI-S score at Endpoint (Week 6).

6.3. Other Efficacy Endpoints

- At each scheduled visit except Endpoint (Week 6), change from Baseline in
  - PANSS total score.
  - CGI-S score.
- At each scheduled visit, change from Baseline in
  - PANSS subscale scores.
  - BNSS total score.
  - MADRS total score.
  - BACS composite score.
  - PSP total score.
  - EQ-5D-5L: visual analog scale (VAS), index score and dimension score.
  - UPSA-B total score.
  - MSQ score.
- PANSS response, defined as a 20% or greater improvement from Baseline in PANSS total score at each scheduled visit.
- Tobacco use at Baseline and Endpoint.

6.4. Safety Endpoints

- The incidence of overall AEs, serious AEs (SAEs), and AEs (or SAEs) leading to discontinuation.
- Observed values and changes from Baseline at each scheduled visit in clinical laboratory tests (hematology, chemistry, and urinalysis), vital signs (including temperature, body weight, body mass index (BMI), waist circumference, blood pressure [supine and standing], pulse rate [supine and standing] and respiration rate) and 12-lead ECG parameters.
- Frequency and severity of suicidal ideation and suicidal behavior based on the C-SSRS.
- Change from Baseline in SAS, BARS and AIMS scores at each scheduled visit.
- Change from Baseline in PSQI global score at each scheduled visit.

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7. INVESTIGATIONAL PLAN

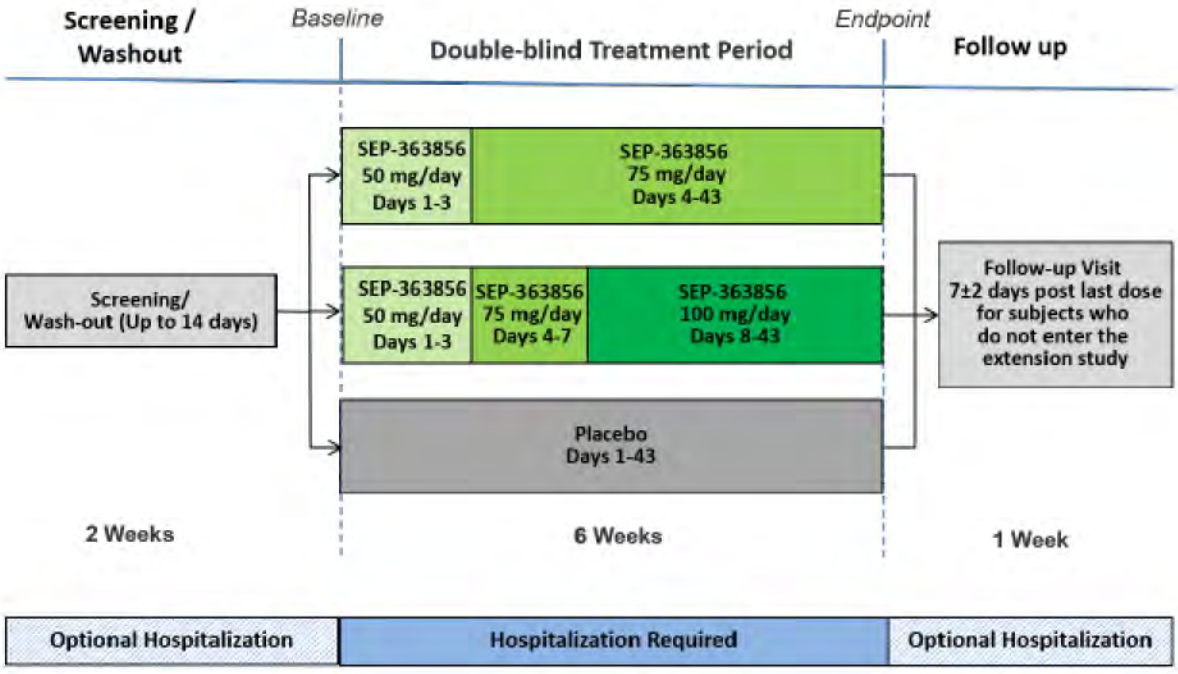
7.1. Overall Study Design

This is a multicenter, randomized, double-blind, parallel-group, fixed-dosed study evaluating the efficacy and safety of two doses of SEP-363856 (75 and 100 mg/day) versus placebo over a 6 week Treatment Period in acutely psychotic subjects with schizophrenia. This study is projected to randomize approximately 462 subjects to 3 treatment groups (SEP-363856 75 mg/day, SEP-363856 100 mg/day, or placebo) in a 1:1:1 ratio. CCI [redacted] Treatment assignment will be stratified by country. Study drug will be taken at the same time each evening at bedtime and may be taken with or without food.

The study will consist of 3 periods: Screening/Washout (up to 14 days), Treatment (6 weeks inpatient), and a Follow-up Visit (7 days after last study drug dose for subjects who discontinue prior to the Week 6 visit [Visit 9] or who complete the study but do not elect to enroll in the open-label extension study [SEP361-303]).

A study schematic is presented in Figure 1. Details of the study assessments and other procedures to be performed at each visit are presented in, Table 2 Schedule of Assessments, and Section 11.8, Study Assessments. If necessary, subjects may return to the clinic at any time for an unscheduled visit.

Figure 1: Study Schematic



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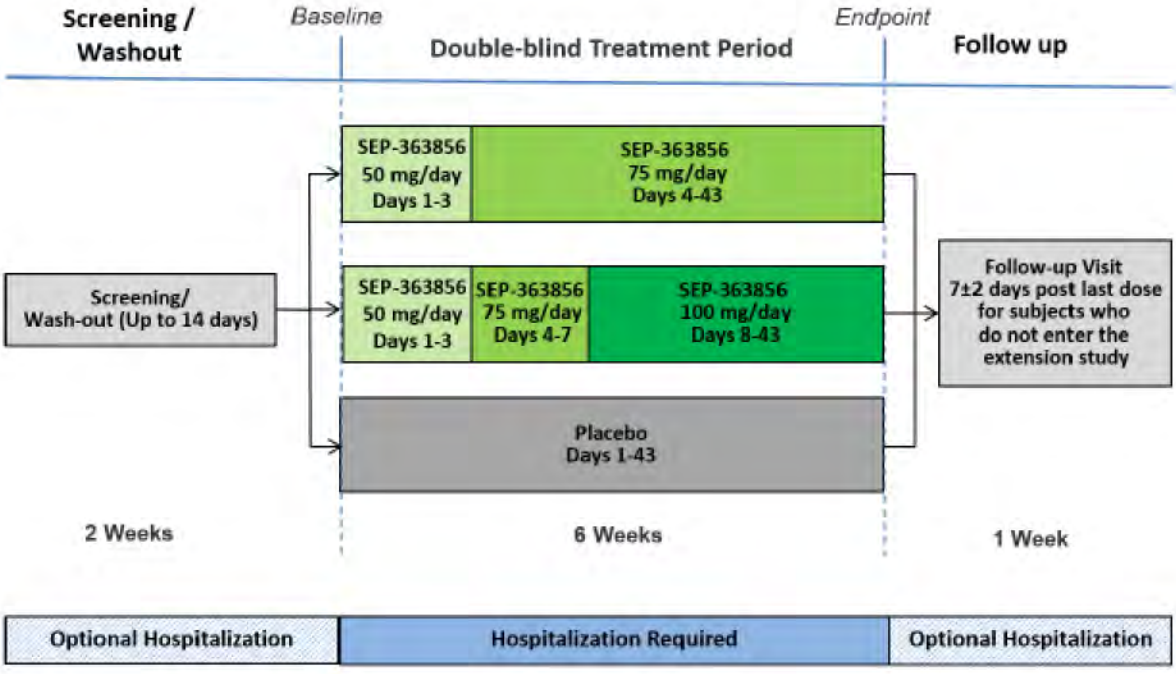

Screening/Washout Period (up to 14 days):

Informed consent will be obtained from each subject before any study procedures are performed. Subjects will be evaluated for eligibility during a screening phase of up to 14 days, during which they will be tapered off all psychotropic medications (except as noted in Section 10.3.4) in a manner that is consistent with labeling recommendations and conventional medical practices.

Subjects may be hospitalized during the screening/washout period at the Investigator's discretion.

The Screening Period may be extended for up to 7 days after approval from the Medical Monitor.

Subjects who screen fail may be re-screened up to two times, if judged appropriate by the Investigator, after discussion with the Medical Monitor. Re-screened subjects will be re-consented, assigned a new subject number, and all Visit 1 procedures will be repeated.

Double-Blind Treatment Period (6 weeks):

Subjects will be inpatient during the entire double-blind Treatment Period through Week 6/Early Termination (ET). Subjects may be eligible for discharge following the Week 6/End of treatment (EOT)/ ET visit.

Randomization/Treatment:

At Baseline (Day 1), subjects who have successfully completed the washout of prior medication and have met the eligibility criteria (see Section 8), will be randomly assigned via an interactive web response system (in a 1:1:1 ratio) to one of three treatment arms: SEP-363856 75 mg/day, SEP-363856 100 mg/day or placebo. Dosing of study drug will begin the evening of the Baseline visit. Treatment will continue once-daily, in the evening at bedtime, for the remainder of the 6-week Treatment Period, during which the procedures outlined in Table 2 will be conducted.

All subjects will receive 50 mg/day or matching placebo for the first three days of the Treatment Period. All subjects will begin receiving 75 mg/day or matching placebo on Day 4. Those subjects assigned to 100 mg/day will begin that dose on Day 8.

All subjects will receive 50 mg/day or matching placebo for the first three days of the Treatment Period. All subjects will begin receiving 75 mg/day or matching placebo on Day 4. Those subjects assigned to 100 mg/day will begin that dose on Day 8. The investigator may request a onetime dose reduction after Day 8 and up to Week 4 (Visit 7) for reasons of safety or tolerability as judged by the Investigator. If the Investigator decides a dose reduction is needed, subjects assigned to the 100 mg/day treatment group will have their dose reduced to 75 mg/day while subjects assigned to 75 mg/day and placebo will remain on their assigned dose (blinded dummy dose reduction for 75 mg/day and placebo). The Investigator and subject will remain blinded to the treatment group assignment and therefore will not know if the dose reduction occurred. Subjects will not be informed that only the 100 mg/day dose group has the possibility of actually receiving a dose reduction. Dose reductions are allowed only once. Subjects unable to tolerate the study medication after a dose reduction (blinded dummy dose reduction or actual dose reduction) will be discontinued from the study. No dose reductions are allowed before Day 8 or after Week 4 (Visit 7). If a dose reduction is required between study visits, a subject will undergo an unscheduled visit for drug dispensation.

Day passes may be granted during the double-blind Treatment Period if the subject is judged by the Investigator to be clinically stable and appropriate for a day pass, and prior approval from the Medical Monitor is obtained. The pass must be limited to a maximum of a half day in duration, and the subject must be accompanied by a staff member. Investigators should follow standard local facility or institutional procedures to ensure subject safety during the time outside of the clinical study center and upon return.

End of Double-Blind Treatment Period:

Subjects will have an End of Treatment (EOT) visit at Week 6 (Visit 9). For subjects who have received study drug and who prematurely discontinue from the study treatment, every effort should be made to complete the final evaluation procedures within 48 hours of the last study drug dose at the early termination (ET) visit.

Subjects who complete the 6-week double-blind Treatment Period will be eligible to participate in a separate open-label extension study (Study SEP361-303) for an additional 52 weeks.

Subjects may be eligible for discharge following the Week 6/ET visit.

Follow-up Period (1 week):

Subjects who discontinue early from the study or complete the study and do not enter the extension study will be required to complete the Follow-up Visit 7 days (± 2 days) post last dose of study drug. For subjects who do not enroll in the extension study, upon completion or early discontinuation from the double-blind Treatment Phase, hospitalization for up to an additional 7 days during the Follow-up Period for the purpose of stabilizing the subject may be allowed after prior authorization from the Medical Monitor.

If a subject requires continued hospitalizations during the Follow-up Period, a serious adverse event (SAE) should be reported once the hospitalization has lasted more than 7 days after the last dose of study drug, unless the hospitalization was due to social reasons (eg, the subject lacks transportation to living environment or lacks stable living environment).

7.2. Treatment Assignment and Blinding

7.2.1. Treatment Assignment

Randomization will be stratified by country. The randomization schedule will be generated by a non-study biostatistician. Once a subject is deemed eligible to be randomized at Day 1, an Interactive web response system (IWRS) will perform treatment assignment. Subjects will be randomized to one of the following treatment groups in a 1:1:1 ratio:

- SEP-363856 75 mg/day for 6 weeks
- SEP-363856 100 mg/day for 6 weeks
- Placebo once daily for 6 weeks

Once a randomization number has been assigned, it cannot be reused.

7.2.2. Blinding

Subjects, Investigators, clinical site staff, persons performing the assessments, clinical operations personnel (including the sponsor's bioanalytical manger), data analysts, and personnel at central laboratories will remain blinded to the identity of the treatment from the time of randomization until database lock and unblinding, using the following methods:

- Randomization data are kept strictly confidential until the time of unblinding in the IWRS, and will not be accessible by anyone else involved in the study with the following exceptions: bioanalytical laboratory personnel involved in the analysis of PK samples, Data and Safety Monitoring Board (DSMB) members involved in regular review of safety data, external statistical staff involved in preparing materials for DSMB reviews, pharmacovigilance department for evaluation and reporting of SAEs, and the Sponsor's clinical trial materials management.
- Prolactin levels will be blinded except for results from Visit 1 (Screening).
- The identity of the treatments will be concealed by the use of study drugs that are all identical in packaging, labeling, schedule of administration and appearance.
- CCI [redacted]

7.2.3. Emergency Unblinding Procedures

In the case of a medical emergency, where knowledge of study drug by the Investigator or an authorized delegate is essential for immediate medical management, a 24-hour code-break service will be available via the IWRS. The date and reason for unblinding are to be documented in the source documents. Any subject for whom the treatment assignment was unblinded is to be discontinued from further study participation. The subject should return for a final study assessment as described in Section 11.8.9. The identity of those individuals at the study site who gain access to the unblinded treatment assignment must be documented. It is mandatory that all personnel who are involved in the unblinding, and who have access to the unblinded treatment assignment, maintain the confidentiality of the information and do not divulge the treatment assignment.

7.3. Rationale

7.3.1. Rationale for the Study Design

This study is designed to confirm and extend the results of Study SEP361-201 and to serve as an adequate, well-controlled study to support marketing applications. The 6-week study duration will provide an adequate timeframe within which to evaluate the effects of SEP-363856 compared to placebo in this subject population. This treatment duration is also consistent with regulatory precedents for the development of a new chemical entity (NCE) for the treatment of patients with schizophrenia.

7.3.2. Rationale for the Dosages

In this study, subjects will be randomized to receive SEP-363856 (75 or 100 mg/day) or placebo for 6 weeks. Titration up to the 75 and 100 mg doses is included to improve tolerability.

Selection of these doses was guided by the results from the development program to-date, including the maximum tolerated dose (MTD) determined for single doses of SEP-363856 administered to subjects with schizophrenia in Study SEP361-105 (100 mg); by the single doses administered to healthy adult subjects in Studies SEP361-103 and SEP361-104 (50 mg) which were found to have robust CNS activity and by Study SEP361-201, which demonstrated a statistically significant difference in change from Baseline to Week 4 in PANSS total score for SEP-363856 (50 to 75 mg/day flexible dose) versus placebo in adults with an acute exacerbation of schizophrenia and which showed that SEP-363856 at doses of 50 to 75 mg/day for up to 28 days was well-tolerated.

The MTD for multiple doses of SEP-363856 in adults with schizophrenia was previously determined to be 75 mg/day (Study SEP361-106). In Study SEP361-106, as more than 50% of SEP-363856 subjects in 100 mg/day cohort (5 of 9 subjects) experienced multiple moderate AEs assessed as related to SEP-363856 the protocol defined MTD for multiple daily oral administration of SEP-363856 to adult subjects with schizophrenia was determined as 75 mg/day. The only moderate AEs assessed as related to SEP-363856 experienced by more than 1 subject in the 100 mg/day dose group were somnolence and dizziness, none of which resulted in treatment discontinuation.

However, in Study SEP361-201, where the majority of subjects received 75 mg/day for 4 weeks, the tolerability and safety profile was shown to be similar to that of placebo. This indicates that a dose higher than 75 mg/day may be tested to maximize efficacy, based on an acceptable expected benefit/risk ratio. In study SEP361-201, subjects were required to receive 50 mg/day for at least 3 days before titrating up to 75 mg/day.

7.3.3. Rationale for the Study Population

The study population will be similar to the population studied in other clinical studies in this indication. It will be comprised of adults aged 18 to 65 years old with a diagnosis of schizophrenia according to DSM-5 who are experiencing an acute exacerbation of psychosis. Subjects will also be required to have had no more than 3 prior hospitalizations for the treatment of an acute exacerbation of schizophrenia or acute psychosis. This study population was selected with the goal of including subjects who are sensitive to change with a pharmacologic treatment, thereby improving signal detection while retaining sample generalizability to the schizophrenia population at large.

This study will also require that female subjects comprise at least 40% of the study population to ensure adequate representation of both sexes, given that there are few apparent sex differences in the prevalence of schizophrenia (Charlson-2018).

7.3.4. Rationale for the Endpoints

The primary and secondary efficacy endpoints will be the change from Baseline to Week 6 on the PANSS total score and CGI-S score, respectively. These endpoints are clinically meaningful

and consistent with regulatory precedents for the development of a NCE for the treatment of patients with schizophrenia.

The other symptom, functional and quality of life assessments were selected to address the potential effectiveness of SEP-363856 on these parameters. The safety assessments and their timing are appropriate to assess the safety of SEP-363856 in adults with schizophrenia over a 6-week period.

7.4. Prevention of Missing Data

In an effort to minimize the number of subjects who are terminated from the study prior to study completion, the following study design and conduct elements are implemented:

- Subjects are required to be inpatient during the double-blind Treatment Period.
- Some concomitant psychotropic medications are allowed, as needed, during study participation.
- Study centers are chosen based on a strong record of enrolling and retaining eligible subjects and producing quality data.
- Study centers are trained on the importance of continued follow-up and on the informed consent process, ensuring subjects understand the commitment they are making, including the intent to complete the trial.
- Data collection is monitored at the site level for adherence during the study.

See Section 15.3.10 for statistical considerations related to missing data.

8. SELECTION OF SUBJECTS

8.1. Subject Inclusion Criteria

To qualify for study participation, the subject must meet all of the following inclusion criteria:

1. Male or female subject between 18 to 65 years of age (inclusive) at the time of consent.
2. Subject must give written informed consent and privacy authorization prior to participation in the study. Separate consent will be obtained from a caregiver or legal guardian if required by local law.
3. Subject must be willing and able to comply with the study procedures and visit schedule, including required hospitalization for the double-blind Treatment Period, and must be able to understand and follow verbal and written instructions.
4. Subject meets DSM-5 criteria for schizophrenia as established by clinical interview (using the DSM-5 as a reference and confirmed using the Structured Clinical Interview at Screening for DSM-5, Clinical Trials Version [SCID-CT]).
5. Information supporting a diagnosis of schizophrenia must be obtained from additional sources to confirm the Screening evaluation of schizophrenia diagnosis. This should include medical records and/or documented correspondence with a treating psychiatrist or mental healthcare provider/staff but can also include information from a reliable informant who is familiar with the subject's psychiatric history (eg, family member, caregiver, case worker, etc.). CCI [redacted]

   Exception: For subjects experiencing their first psychotic episode or who have not previously been seen by a psychiatrist or mental healthcare provider, documentation of schizophrenia diagnosis by a psychiatrist or mental healthcare provider other than the trial Investigator or Sub-Investigator is required.
6. Subject must have a CGI-S score ≥ 4 at Screening and Baseline.
7. Subject must have a PANSS total score ≥ 80 and a PANSS item score ≥ 4 on 2 or more of the following PANSS items: delusions, conceptual disorganization, hallucinations, and unusual thought content at Screening and Baseline.
8. Subject has an acute exacerbation of psychotic symptoms (persisting no longer than 2 months prior to providing informed consent for this study).
9. Subject has marked deterioration of functioning in one or more areas, such as occupational, social, or personal care or hygiene.

10. Subject has had no more than 3 prior lifetime inpatient hospitalizations for the treatment of an acute psychotic episode or exacerbation of schizophrenia (not including hospitalization at the time of Screening, during Screening or at Baseline). Hospitalization history must be informed by sources other than the subject's own report. This should include medical records and/or documented correspondence with a treating psychiatrist or mental healthcare provider/staff but can also include information from a reliable informant who is familiar with the subject's psychiatric history (eg, family member, caregiver, case worker, etc.). CCI [redacted]
11. Subject's body mass index (BMI) must be 18 kg/m^2 to 40 kg/m^2 (inclusive) at Screening.
12. Female subjects must have a negative serum pregnancy test at Screening.
13. Female subjects of childbearing potential must agree to use highly effective and reliable contraception throughout the study and for at least 30 days after the last dose of study drug has been taken. In the Investigator's judgment, the subject will adhere to this requirement. Contraception requirements are detailed in Section 10.5.
14. Male subjects agree to avoid fathering a child and to use highly effective methods of birth control from screening until at least 30 days after the last study drug administration. Contraception requirements are detailed in Section 10.5.
15. Subject is, in the opinion of the Investigator, generally healthy based on screening medical history, PE, neurological examination, vital signs, ECG, and clinical laboratory values (hematology, chemistry and urinalysis).
16. Subject has had a stable living arrangement at the time of Screening and agrees to return to a similar living arrangement after hospital discharge. This criterion is not meant to exclude subjects who have temporarily left a stable living arrangement (eg, due to psychosis). Such subjects remain eligible to participate in this protocol. Chronically homeless subjects are not eligible for this study.
17. Subject's eligibility confirmed through formal adjudication process (See Section 10.9).

8.2. Subject Exclusion Criteria

Subjects who meet any of the following criteria will be excluded in the study:

1. Subject has had a decrease (improvement of symptoms) of ≥ 20% on the PANSS total score between Screening and Baseline (See Section 25, Appendix VI).
2. Subject has been hospitalized for more than 2 consecutive weeks immediately before screening, unless the hospitalization was for reasons unrelated to acute psychotic exacerbation. For example, a subject who is in a long-term hospital setting, is experiencing an acute exacerbation and is transferred to an acute treatment unit is eligible for the study.
3. Subject has a DSM-5 diagnosis or presence of symptoms consistent with a DSM-5 diagnosis other than schizophrenia. Exclusionary disorders include but are not limited to alcohol use disorder (within past 12 months or for a total of ≥ 10 years during the subject's lifetime), substance (other than nicotine or caffeine) use disorder within past

12 months or for a total of ≥ 10 years during the subject's lifetime, major depressive disorder, bipolar I or II disorder, schizoaffective disorder, obsessive compulsive disorder, and posttraumatic stress disorder. Symptoms of mild to moderate mood dysphoria or anxiety are allowed so long as these symptoms are not the primary focus of treatment.

4. Subject is judged to be resistant to antipsychotic treatment by the Investigator, based on failure to respond to 2 or more marketed antipsychotic agents within a 1-year period prior to Screening, given at adequate dose as per labeling, for at least 4 weeks.
5. Subject answers "yes" to "Suicidal Ideation" Item 4 (active suicidal ideation with some intent to act, without specific plan) or Item 5 (active suicidal ideation with specific plan and intent) on the C-SSRS assessment at Screening (ie, in the past one month) or Baseline (ie, since last visit).
6. Subject is at significant risk of harming self, others, or objects based on Investigator's judgment.
7. Subject has attempted suicide within 6 months prior to screening.
8. Subject is involuntarily hospitalized.
9. Subject has received treatment with a psychotropic medication or herbal supplement within 3 days or 5 half-lives (whichever is longer) prior to randomization or anticipates the need for psychotropic medications or herbal supplements during their participation in this study, with the exception of the medications specified in Section 10.3.4. The following medications have additional washout requirements as specified below:
    - Monoamine oxidase inhibitors (MAOIs) must be discontinued at least 28 days prior to randomization.
    - Fluoxetine or fluoxetine/olanzapine combination must be discontinued at least 28 days prior to randomization.
    - Clozapine used at 200 mg/day or less for insomnia, agitation, or anxiety must be discontinued prior to randomization over a 1 to 2-week period, as judged to be safe by the investigator. Subjects with a history of treatment with clozapine for any reason at doses greater than 200 mg/day or at doses less than or equal to 200 mg/day for a usage other than insomnia, agitation, or anxiety are excluded from study participation.
    - Depot neuroleptics must have been discontinued at least one treatment cycle or at least 30 days (whichever is longer) prior to randomization visit.
10. Subject who received a total dose of antipsychotic medication equivalent to ≥ 12.0 mg/day of haloperidol within the current episode (See Section 21, Appendix II). Subject may be eligible if such treatment is less than 2 weeks in duration after consultation with the Medical Monitor.
11. Subject has received electroconvulsive therapy treatment within the 3 months prior to Screening or is expected to require electroconvulsive therapy (ECT) during the study.
12. Subject has any clinically significant unstable medical condition or any clinically significant chronic disease that in the opinion of the Investigator, would limit the subject's ability to complete and/or participate in the study:

a) Hematological (including deep vein thrombosis) or bleeding disorder, renal, metabolic, endocrine, pulmonary, gastrointestinal, urological, cardiovascular (including unstable hypertension), hepatic, neurologic, or allergic disease that is clinically significant or unstable (except for seasonal allergies at time of dosing) **Note: Any subject with a known cardiovascular disease or condition, including hypertension, (even if under control and considered stable) must be discussed with the Medical Monitor before being randomized in the study.**

b) Subject has a history of neuroleptic malignant syndrome.

c) Subject has a history of malignancy within 5 years prior to the Screening visit, except for adequately treated basal cell or squamous cell skin cancer or in situ cervical cancer.

d) Subject has a history of a pituitary tumor of any duration.

e) Subject has a history of a condition or previous gastrointestinal surgery (eg, cholecystectomy, vagotomy, or bowel resection) that may interfere with drug absorption, distribution, metabolism, excretion, gastrointestinal motility, or pH.

f) Subject has a history of malabsorption.

g) Subject has a clinically significant abnormal 12-lead ECG that may jeopardize the subject's ability to complete the study or that may confound study results as determined by the Investigator, or a screening centrally overread 12-lead ECG demonstrating any one of the following: heart rate > 100 beats per minute, heart rate < 50 beats per minute, QRS > 120 ms, QT interval corrected for heart rate using Fridericia's formula (QTcF) > 450 ms (males), QTcF > 470 ms (females), or PR > 220 ms. Subjects with an ECG that has a centrally overread overall interpretation of "abnormal, significant" or "potentially clinically significant" must be discussed with the Medical Monitor.

h) Subjects with known history of human immunodeficiency virus (HIV) seropositivity.

i) Subject has type I diabetes mellitus or insulin-dependent type II diabetes mellitus.

13. Female subject who is pregnant or lactating.

14. Subject has a history of allergic reaction or suspected sensitivity to any substance that is contained in the formulation.

15. Subject with a supine systolic blood pressure ≥ 140 mmHg and/or supine diastolic blood pressure ≥ 90 at Screening or Baseline. A repeat blood pressure measurement is allowed once during the Screening Period and once at Baseline. The repeat measurements at Screening can be used to determine eligibility. The repeat blood pressure measurement at Screening can be conducted on a different day within the screening period, if needed.

16. Subject has any clinically significant abnormal laboratory value(s) at Screening (hematology, chemistry, and urinalysis) as determined by the Investigator. (Note: Retesting is allowed during the Screening Period and the retest used to determine eligibility after approval from the Medical Monitor; however, the Screening Period will not be extended to accommodate repeat laboratory tests, unless repeat tests are needed due to a technical issue with laboratory sample processing or a shipment or testing delay

at the central laboratory. Abnormal findings of questionable significance will be discussed with the Medical Monitor prior to including subject.)

17. Subject demonstrates evidence of acute hepatitis, clinically significant chronic hepatitis, or evidence of clinically significant impaired hepatic function through clinical and laboratory evaluation. Subjects who test positive for hepatitis C antibody at Screening and have a positive or indeterminate confirmatory test for hepatitis C are excluded. Subjects who test positive for hepatitis B surface antigen at screening are excluded.
18. Subjects with ALT or AST $\geq$ 3 times the upper limit of the reference ranges provided by the central laboratory at Screening.
19. Subject has a serum blood urea nitrogen (BUN) or serum creatinine (Cr) value $\geq$ 1.5 times the upper limit of normal of the reference range provided by the central laboratory at Screening.
20. Subjects with fasting blood glucose at Screening $\geq$ 126 mg/dL (7.0 mmol/L) or HbA_{1c} >7% at Screening.
21. Subject has a prolactin concentration > 200 ng/mL at Screening. **NOTE:** Subjects with prolactin levels > 100 ng/mL and $\leq$ 200 ng/mL at Screening are eligible only after discussion with the Medical Monitor to ensure exclusion of non-psychotropic drug-related causes of elevated prolactin levels.
22. Subject tests positive for drugs of abuse at Screening. However, a positive test urine drug screen may not result in exclusion of subjects if the Investigator determines that the positive test is as a result of prescription medicine(s). Subjects who test positive for cannabinoids (tetrahydrocannabinol or cannabidiol) at screening are excluded.
23. Subject has received an investigational drug product or device within 90 days prior to signing informed consent or has participated in more than 3 studies in psychiatric indications of investigational drug products or devices within their lifetime.
24. Subject has previously received SEP-363856 or was previously enrolled in a SEP-363856 clinical study.
25. Subject is a staff member or the relative of a staff member.
26. Subject is in the opinion of the Investigator, unsuitable in any other way to participate in this study.

9. STUDY DRUG MATERIALS AND MANAGEMENT

9.1. Description of Study Drug

Table 5: Investigational Product

Attribute	Investigational Product			
Product name	SEP-363856	SEP-363856	SEP-363856	Placebo
Dosage form	Tablet	Tablet	Tablet	Tablet
Unit dose	50 mg	75 mg	100 mg	NA
Route of administration	Oral	Oral	Oral	Oral
Physical description	Yellow oval tablet	Yellow oval tablet	Yellow oval tablet	Yellow oval tablet
Active Pharmaceutical ingredient (API)	SEP-363856-01 (hydrochloride salt)	SEP-363856-01 (hydrochloride salt)	SEP-363856-01 (hydrochloride salt)	NA
Excipients	-Microcrystalline cellulose -Mannitol -Sodium starch glycolate -Magnesium stearate Film coating: -Hydroxypropyl methylcellulose -Hydroxypropyl cellulose -Titanium dioxide -Yellow iron oxide Carnauba wax	-Microcrystalline cellulose -Mannitol -Sodium starch glycolate -Magnesium stearate Film coating: -Hydroxypropyl methylcellulose -Hydroxypropyl cellulose -Titanium dioxide -Yellow iron oxide Carnauba wax	-Microcrystalline cellulose -Sodium starch glycolate -Magnesium stearate Film coating: -Hydroxypropyl methylcellulose -Hydroxypropyl cellulose -Titanium dioxide -Yellow iron oxide Carnauba wax	-Microcrystalline cellulose -Mannitol -Sodium starch glycolate -Magnesium stearate Film coating: -Hydroxypropyl methylcellulose -Hydroxypropyl cellulose -Titanium dioxide -Yellow iron oxide Carnauba wax

9.2. Study Drug Packaging and Labeling

9.2.1. Package Description

Study drug will be provided in one-week blister cards containing 9 tablets of SEP-363856 (7 days + 2 extra days).

9.2.2. Labeling Description

All packaging for the study medications will be labeled with:

- Protocol number
- Sponsor's name and address

- Compound/Code or name of investigational drug and dosage form
- Content (eg, number of tablets)
- Investigational Drug/caution statement
- Batch number
- Blank space to record visit number
- Blank space for subject identifiers
- Period of use (as required)
- Unique medication /kit ID number
- Investigator information (if needed)

9.3. Study Drug Storage

All study drug should be stored at 15°C to 25°C (59°to 77°F). Excursions of 9°C to 30°C (48°F to 86°F) are permitted during shipment of study drug to investigational sites.

9.4. Dispensing of Study Drug

An Interactive Web Response System (IWRS) will be used to manage subject screening and randomization. The IWRS is an integrated web-based subject and drug management system.

Study drug blister cards will be assigned by the IWRS based on the treatment schedule. The IWRS will generate instructions for which blister card ID to assign to a subject. IWRS drug dispensing guidelines should be followed for dispensing study drug to the subject. A specific user manual will be supplied.

Study drug will be administered by site staff to the subjects on an inpatient basis. Subjects will take one tablet of study drug per day at approximately the same time each evening at bedtime. Study drug may be taken without regard for food.

9.5. Study Drug Accountability

The Investigator or designee is responsible for maintaining adequate and up to date records of drug disposition that includes the dates, quantity, and use by subjects.

Upon receipt of study drug, the Investigator or designee will inspect the supplies and confirm receipt of the shipment in the IWRS, confirming the date of receipt, inventory and condition of study drug received.

The IWRS will also be used for the accountability of the study drug at the clinical site. The Investigator or designee will maintain the records for accountability within IWRS, including study drug dispensation, return and availability of study drug received. The Investigator or designee will collect and document the status of all used and unused study drug from study subjects at appropriate study visits.

9.6. Study Drug Handling and Disposal

The Investigator or designee is responsible for storing the study drug in a secure location. Study drug should be maintained under the strict control of qualified site staff at all times. Proper handling and storage guidelines should be followed.

If the study is stopped for any reason or completed, all unused supplies will be returned to the Sponsor, unless other instructions are provided in writing by Sponsor/CRO.

The Investigator or designee is required to return all used and unused study drug to the Sponsor or designee as instructed. The Investigator or designee is required to maintain copies of study drug shipping receipts, drug accountability records, and records of return or final disposal of the study drug in accordance with local regulatory requirements.

Study drug will not be dispensed to any person who is not a study subject under this protocol.

10. TREATMENT OF SUBJECTS

10.1. Study Medication

All doses of study drug will consist of either matching SEP-363856 50 mg, 75 mg or 100 mg tablets or matching placebo tablets (in order to maintain blinding) administered orally once daily and will be supplied as described in Section 9.

Subjects will take study drug at approximately the same time each evening at bedtime without regard for food beginning on Day 1 and continuing through Day 42.

10.2. Treatment Compliance

The Investigator will record the dose of the study drug and the date and time of the initial and final administration for each visit.

Compliance must be monitored closely and determined at each visit. Compliance will be calculated by counting tablets and dividing the actual number of doses taken (per tablet count) by the number of doses the subject should have taken within a visit period and multiplying by 100. All subjects will be reminded of the importance of strict compliance with taking study drug for the effectiveness of treatment and for the successful outcome of the study. Subjects who miss more than 25% of scheduled doses or take more than 125% of the scheduled doses will be considered noncompliant. Evidence of noncompliance must be immediately reported to the Clinical Research Associate (CRA) and/or Medical Monitor.

10.3. Prior and Concomitant Medications

Prior medications, including the use of psychotropic medication during the previous 3 years, and any other medication taken during the previous 60 days will be recorded at Visit 1 (Screening).

Details on all medications taken in the 60 days prior to Screening (including dosing changes) will be recorded. For psychotropic medications taken prior to that 60-day period, approximate start and stop dates of each unique psychotropic medication will be recorded, along with the maximum daily dose of the psychotropic medication ever taken during the specified time period (ie, it is not required to capture every psychotropic dose change during this period).

Every effort should be made to collect medical and/or pharmacy records for psychotropic medications used in the past 3 years and non-psychotropic medications used in the past 60 days on the eCRF. However, if medical records cannot be obtained, prior medications are to be reported based on subject and caregiver/informant report.

Thereafter, any changes in concomitant medications or new medications added up to the Follow-up Visit from the study will be recorded. At a minimum, the following information on prior and concomitant medications will be recorded on the case report form (CRF): Medication name, dose, frequency, route, start date and time, stop date and time, and indication.

Information on the format and version of the coding dictionary is provided in the Data Coding Guidelines. All medications will be coded using World Health Organization – Drug Dictionary (WHO-DD).

10.3.1. Prior Medications

Treatment with oral psychotropic medications and any other medications with a propensity for psychotropic effects (with the exception of the medications described in Section 10.3.4) must be discontinued for at least 3 days or 5 half-lives (whichever is longer) prior to randomization in a manner that is consistent with conventional medical practice. The following medications have additional washout requirements as specified below:

- Monoamine oxidase inhibitors (MAOIs) must be discontinued at least 28 days prior to randomization.
- Fluoxetine or fluoxetine/olanzapine combination must be discontinued at least 28 days prior to randomization.
- Clozapine used at 200 mg/day or less for insomnia, agitation, or anxiety must be discontinued prior to randomization over a 1 to 2-week period, as judged to be safe by the investigator. Subjects with a history of treatment with clozapine for any reason at doses greater than 200 mg/day or at doses less than or equal to 200 mg/day for an indication other than insomnia, agitation, or anxiety are excluded from study participation.
- Depot neuroleptics must have been discontinued at least one treatment cycle or at least 30 days (whichever is longer) prior to the randomization visit.

Treatment with sedative hypnotics is permitted during the screening period but should be tapered as clinically appropriate to conform with and adequately prepare the subject for the protocol-specified limitations applicable to these agents following randomization (see Section 10.3.4). Subjects should not be taken off their current effective medications for treatment of schizophrenia for purposes of participating in this study.

Treatment with medications used to treat movement disorders must be discontinued at least 1 day prior to randomization.

10.3.2. Prohibited Medications

Psychotropic medications and medications with a propensity for psychotropic effects are not permitted during the 6-week Treatment Period up through the End of Treatment (EOT) Visit, except for the medications discussed in Section 10.3.4.

The use of herbal supplements, dietary supplements or other complementary or alternative medications for treating psychiatric indications are not permitted during the 6-week Treatment Period up through the EOT visit.

Use of psychotropic medications, herbal/dietary supplements, or other complementary/ alternative medications for treating psychiatric indications after the last dose of study medication is permitted for those not continuing into the extension study (SEP361-303) provided they are not administered prior to the final PANSS assessment.

Subjects who are administered a psychotropic medication (other than the study drug and the acceptable medications described in Section 10.3.4) for the purposes of treating an exacerbation of symptoms associated schizophrenia or due to lack of efficacy of the study treatment will be discontinued from the study.

10.3.3. Prohibited Therapies

Subjects must not receive electroconvulsive therapy (ECT) treatment within the 3 months prior to Screening nor during the Treatment Period up through the Follow-up Visit. Subjects who received ECT treatment during the Treatment Period will be discontinued from the study.

10.3.4. Allowed Concomitant Psychotropic Medications

Treatment with benztropine (benzotropine outside the United States [US]) up to 6 mg/day is permitted, as needed, for movement disorders. In cases where benztropine is not available or a subject has had an inadequate response or intolerability to benztropine treatment, the following medications may be used to treat acute extrapyramidal symptoms (EPS): biperiden (up to 16 mg/day) or trihexyphenidyl (up to 15 mg/day) or diphenhydramine (up to 100 mg/day). Treatment with propranolol (up to 120 mg/day) is permitted as needed for akathisia. These allowed medications for the treatment of EPS and akathisia may be given in any formulation (oral, IM or IV) as deemed appropriate by the Investigator. Medications used to treat movement disorders should not be given prophylactically. They are to be tapered and discontinued at least 1 day prior to randomization but may be reinstated if symptoms emerge post-randomization during the study.

Concomitant use of lorazepam, temazepam, eszopiclone, zaleplon, zolpidem and zolpidem CR is permitted at the discretion of the Investigator with the following restrictions:

- Oral lorazepam (or equivalent benzodiazepine) is permitted for clinically significant anxiety/agitation or as a sedative/hypnotic up to a maximum daily dose of 6 mg/day. Intramuscular lorazepam is permitted up to 4 mg/day only for acute anxiety/agitation, as clinically indicated. Lorazepam should be used sparingly, when clinically required, per Investigator judgment.
- Temazepam (≤ 30 mg/day), eszopiclone (≤ 3 mg/day), zopiclone (≤ 7.5 mg/day), zaleplon (≤ 20 mg/day), zolpidem (≤ 10 mg/day), and zolpidem CR (≤ 12.5 mg/day) may be administered at bedtime for insomnia, as needed.
- Medications that are used for insomnia should be administered no more than once nightly and should not be used in combination.
- Medications used for the treatment of anxiety/agitation and insomnia (eg, lorazepam and zolpidem) should not be used in close temporal proximity (defined as administration within 2 hours of each other).

In regions that do not have the above specified drugs available, similar drugs at equivalent dosages will be permitted in consultation with the Medical Monitor.

The date and time of the last dose of any concomitant psychotropic medication(s) taken prior to efficacy assessments must be recorded at each visit. Subjects should be encouraged to avoid taking any psychotropic medication (or any agents that my cause sedation) within 8 hours of efficacy assessments.

Opioids for the treatment of pain may be allowed in rare cases for a limited period of time with prior authorization from the Medical Monitor.

10.3.5. Concomitant Non-psychotropic Medications

Non-psychotropic medications used to treat mild, chronic medical conditions may be used during screening and after randomization if the dose and regimen have been stable (± 25% total daily dose) for at least 30 days prior to screening. The dose for the concomitant medication may change, as needed, after randomization (or be discontinued). This includes β-adrenergic antagonists used to treat stable hypertension. Routine vaccines (ie, seasonal influenza, pneumonia, etc.) are allowed based on the Investigator's judgment. Female subjects may use contraception as detailed in Section 10.5.

Use of non-prescription pain medications (eg, aspirin, acetaminophen/paracetamol) are allowed during all phases of the study provided these medications do not have a propensity for psychotropic effects.

The Medical Monitor should be consulted, if possible, before administering medications for short-term treatment of an acute medical condition. If medications are administered for short-term treatment of an acute medical condition without prior consultation with the Medical Monitor, the Medical Monitor is to be informed of such medication use as soon as possible and the appropriateness for the subject to continue in the study should be discussed with the Medical Monitor.

10.4. Other Restrictions

Subjects must abstain from alcohol from clinic admission through the end of the study.

10.5. Contraception Requirements

Female subjects who participate in this study must be of:

- Non-childbearing potential (ie, physiologically incapable of becoming pregnant), which includes:
  - Women who have had a hysterectomy, bilateral oophorectomy, bilateral salpingectomy, bilateral tubal ligation or bilateral tubal occlusion (as determined by subject's medical history)

    OR
  - Postmenopausal females, defined as at least 12 months of spontaneous amenorrhea and confirmed by follicle stimulating hormone {FSH} concentrations within postmenopausal range as determined by the central laboratory

-OR-

- Childbearing potential with a negative serum pregnancy test at screening and satisfying one of the following requirements:
  - Completely abstinent from intercourse as part of the preferred and usual lifestyle of the subject. Periodic abstinence (eg, calendar, ovulation, symptothermal, post-ovulation methods) and the withdrawal method are not acceptable methods of contraception. Subject must have been abstinent for at least 60 days prior to administration of the first dose of study drug, throughout the Treatment Period

and for a minimum of 30 days after completion or premature discontinuation from the study drug.

- Use of highly effective methods of contraception during the Treatment Period and for 30 days after last dose of study drug. Highly effective forms of contraception include:
  - Subcutaneous hormonal implant (such as Norplant®) implanted at least 90 days prior to Screening;
  - Injectable hormonal contraception (such as medroxyprogesterone acetate injection) given at least 14 days prior to Screening;
  - Oral or transdermal hormonal contraception used as directed for at least 30 days prior to Screening.
  - Vaginal ring (eg, NuvaRing®) used as directed for at least 30 days prior to Screening.
  - Intrauterine device implanted at least 30 days prior to Screening.
  - Intrauterine hormone-releasing system implanted at least 30 days prior to Screening.
  - Two barrier methods used in combination (eg, condom and spermicide or diaphragm with spermicide). Note: a female condom and a male condom should not be used together due to friction between the 2 barrier methods reducing effectiveness of contraception.

Post-coital methods of contraception are not permitted.

Male subjects with a female partner(s) of childbearing potential must agree to avoid fathering a child and must be surgically sterile (with the appropriate post-vasectomy documentation of the absence of sperm in the ejaculate) or use highly effective methods of contraception from Screening until at least 30 days after the last dose of study drug. Male subjects must also refrain from donation of semen/sperm 30 days prior to administration of the first dose of study drug, during the Treatment Period and for 30 days after last dose of the study drug.

10.6. Description of Study Periods, Hospital Discharge, and Day Passes

10.6.1. Hospital Discharge During the Study

To facilitate enrollment of acutely ill subjects and to optimize treatment compliance, hospitalization period is mandated during the double-blind Treatment Period. Subjects are eligible for hospital discharge beginning at Visit 9 (Week 6; Day 43) or upon early termination if they meet all of the following criteria:

1. The subject is considered by the Investigator to be clinically stable and appropriate for discharge to an outpatient or community setting.
2. There is no evidence of imminent danger to self or others.

3. Subject answers "no" to "Suicidal Ideation" Item 4 (active suicidal ideation with some intent to act, without specific plan) and Item 5 (active suicidal ideation with specific plan and intent) on the C-SSRS at time of evaluation.
4. An outpatient environment is available that ensures continued safety for the subject and continued contact with the treatment team for the remainder of the protocol.

Discharge under these conditions is permitted after completion of all assessments at Visit 9 (Day 43) or the ET Visit. Subjects may participate in day-hospital or outpatient programs after hospital discharge. If the subject does not meet the discharge criteria at Visit 9 or early termination, hospitalization will be allowed for up to an additional 7 days during the Follow-up Period to stabilize the subject, if necessary. Prior authorization for this additional hospitalization must be provided by the Medical Monitor. If a subject requires continued hospitalizations during the Follow-up Period, a serious adverse event (SAE) should be reported once the hospitalization has lasted more than 7 days after the last dose of study drug, unless the hospitalization was due to social reasons (eg, the subject lacks transportation to living environment or lacks stable living environment). After completion of the Follow-up Visit or upon study discontinuation, all subjects will be referred for appropriate continued treatment and follow-up care as determined by the Investigator.

10.6.2. Day Passes

Day passes may be granted during the study if the subject is judged by the Investigator to be clinically stable and appropriate for a day pass, and prior approval from the Medical Monitor is obtained. The pass must be limited to a half day in duration, and the subject must be accompanied by a staff member. Investigators should follow standard local facility or institutional procedures to ensure subject safety during the time outside of the clinical study center. The reason for and duration of the day pass as well as Medical Monitor approval must be documented. Subjects will receive an unscheduled urine drug screen upon return to the site.

10.7. Guidance for Overdose

Potential overdose to SEP-363856 has not been evaluated. The effects of an overdose of SEP-363856 are unknown and there is no known treatment in case of overdose. Appropriate supportive measures should be instituted, and close medical supervision and monitoring should be used in the case of pharmacological effects or overdose until the subject recovers. Consider the possibility of multiple-drug overdose.

10.8. Dietary Guidelines

While subjects are confined to the clinic meals and snacks will be provided at the discretion of the clinical site.

10.9. Eligibility Adjudication Process

All subjects will be evaluated by the Sponsor and/or designee to determine their eligibility for the study prior to randomization.

Sites will complete a form for each subject in screening, which provides information that supports the subject's appropriateness for participation in the study. Each form must be approved by the Sponsor or designee prior to the subject being randomized.

In addition, audio recordings of the Screening PANSS scale may be reviewed by the Sponsor's designee with clinical expertise in PANSS scale administration. The outcome of the PANSS audio recording review may be utilized by the Sponsor or designee to evaluate the subject's eligibility.

11. STUDY ASSESSMENTS

A study schematic is presented in Figure 1. A summary of assessments to be conducted at each visit is presented in Table 2.

11.1. Demographics and Baseline Characteristics

Demographics (date of birth, age, sex, ethnicity, race), prior and current medications, and medical and psychiatric history will be collected.

A medical and psychiatric history will be obtained by the Investigator or qualified designee as listed on the Form FDA 1572. If the subject's historical medical care was provided at another institution or location, documented efforts must be made to obtain these outside records to verify that the subject meets all inclusion and none of the exclusion criteria. This must be accomplished during the screening period. Alcohol and substance abuse history should also be obtained and documented in the subject's study chart. The Medical History will subsequently be coded using the Medical Dictionary for Regulatory Activities (MedDRA).

For US sites only, subjects will be checked for multiple study enrollment at screening by clinical site staff using available registries of subjects participating in clinical trials. US sites will be provided training.

11.1.1. Healthcare Resource Utilization

Healthcare resource utilization will be assessed by recording the following at Baseline:

- number of physician office visits, emergency room visits, and hospitalizations (total number and number related to schizophrenia) in the previous 3 months
- length of each hospital stay in the past 3 months
- employment status in the past 3 months
- the average number of hours a caregiver(s) spends helping the subject per week (past 3 months)

11.2. Prior and Concomitant Medication Review

See Section 10.3 for a complete description of medications permitted during the study. Prior and concomitant medications will be recorded at Visit 1 (Screening). Thereafter, any changes in concomitant medications or new medications added up to Visit 10 or discontinuation from the study will be recorded.

At a minimum, the following information on prior and concomitant medications will be recorded on the CRF: Medication name, dose, frequency, route, start date, stop date, and indication.

The prior and concomitant medications will subsequently be coded using the World Health Organization Drug Dictionary (WHO-DD).

11.3. Structured Clinical Interview for DSM-5 Axis I Disorders-Clinical Trials version (SCID-CT)

The SCID-5-CT is a modified version of the SCID developed for use in clinical trials. It is a semi-structured interview for the purpose of making a DSM-5 diagnosis (First-2015). Clinicians administering the SCID should be familiar with the DSM-5 classification and diagnostic criteria. The SCID-5-CT will be administered by a qualified rater at the research site listed on Form FDA 1572 with at least 2 years of clinical experience with schizophrenia patients. The administration time is approximately 30 - 40 minutes.

11.4. Efficacy Assessments

Raters will receive specific training regarding each assessment prior to study initiation.

11.4.1. Positive and Negative Syndrome Scale (PANSS)

The PANSS is an interview-based measure of the severity of psychopathology in adults with psychotic disorders. The measure is comprised of 30 items and 3 subscales: the Positive subscale assesses hallucinations, delusions, and related symptoms; the Negative subscale assesses emotional withdrawal, lack of motivation, and similar symptoms; and the General Psychopathology subscale addresses other symptoms such as anxiety, somatic concern, and disorientation. An anchored Likert scale from 1 - 7, where values of 2 and above indicate the presence of progressively more severe symptoms, is used to score each item. Individual items are then summed to determine scores for the 3 subscales, as well as a total score. A Composite scale score (Positive scale score minus Negative scale score) can also be calculated to show the relative valence of positive and negative symptoms. Total time required for the PANSS interview and scoring is approximately 30 to 40 minutes (Kay-1994, Opler-1992; Perkins-2000). PANSS raters will be required to meet specific training and education criteria before they are certified to rate for this study. The PANSS requires input from an informant (eg, caregiver, relative, friend, case worker, hospital staff). PANSS interviews will be audio recorded and the recording may be reviewed by Sponsor's designee to monitor the quality of the rater interviews, where allowed by local/regional regulations. No identifying information will be associated with the audio recording.

11.4.2. Clinical Global Impressions – Severity Scale (CGI-S)

The CGI-S is a clinician-rated assessment of the subject's current illness state on a 7-point scale, where a higher score is associated with greater illness severity. Following a clinical interview, the CGI-S can be completed in 1 to 2 minutes. The CGI-S will be administered by a qualified rater at the site.

11.4.3. Brief Negative Symptom Scale (BNSS)

The BNSS is a rating scale to measure the current level of severity of negative symptoms in schizophrenia and schizoaffective disorder (Kirkpatrick-2011). The measure is comprised of 13 individual items and 6 subscale scores (blunted affect, alogia, avolition, anhedonia, asociality, and distress). The 6 subscale scores provide a summary score and the 13 individual items provide a composite total score (ranging from 0 to 78). Each of the items are scored on a Likert-type 7-point scale from 0 - 6, where values of 0 indicates symptom is absent and a value of 6 means

the symptom is a severe form. The number of items varies per subscale. BNSS raters will be required to meet specific training and education criteria before they are certified to rate for this study.

11.4.4. Montgomery-Asberg Depression Rating Scale (MADRS)

The MADRS is a clinician-rated assessment of the subject's level of depression. The measure contains 10 items that measure apparent and reported sadness, inner tension, reduced sleep and appetite, difficulty concentrating, lassitude, inability to feel, and pessimistic and suicidal thoughts. Each item is scored in a range of 0 to 6 points, with higher scores indicating increased depressive symptoms. The Structured Interview Guide for the MADRS (SIGMA) (Williams-2008) will be used for the administration of the MADRS assessment. The MADRS will be administered by a qualified rater at the site.

11.4.5. Brief Assessment of Cognition in Schizophrenia (BACS)

The BACS assesses six domains of cognition; verbal memory/learning, working memory, motor function, verbal fluency, speed of processing, and executive function. Administration time is approximately 30 minutes.

An electronic tablet-based version of the traditional BACS, called the BAC App, will be used in this study. The BAC App was developed to allow standardized presentation of task instructions and stimuli, audio-recording of responses, and automatized scoring and data management. The BAC App provides a composite measure of cognition, as well as individual scores for each of the cognitive domains noted below. It has been clinically validated in schizophrenia and has demonstrated equivalence with the original pen-and-paper measure (Atkins-2017).

- Verbal Memory/Learning is assessed with the Verbal Memory task. Subjects are presented with a list of 15 words and asked to recall as many as possible. This procedure is repeated 5 times. The outcome measure is the number of words recalled.
- Working Memory is assessed with the Digit Sequencing task. Subjects are presented with auditory clusters of numbers (eg, 936) of increasing length and asked to tell the rater the numbers in order from lowest to highest. The outcome measure is the number of correct responses.
- Motor Function is assessed with the Token Motor task. Subjects are presented with tokens and asked to drag them to a center container as quickly as possible for 60 seconds. The outcome measure is the number of tokens correctly dragged into the container.
- Verbal Fluency is assessed with Semantic Fluency and Letter Fluency tasks. Subjects are given 60 seconds to generate as many words as possible in a given category (semantic) or for a given letter of the alphabet (letter). The outcome measure for each fluency test is the number of words generated.
- Speed of Processing is assessed with the Symbol Coding task. Subjects are provided a key and asked to fill the corresponding number beneath a series of symbols as quickly as possible within 90 seconds. The outcome measure is the number of correct items.

- Executive Function is assessed with the Tower of London task. Subjects are asked to give the minimum number of times the balls in one picture would need to be moved in order to make the arrangement of balls identical to that in the opposing picture. The outcome measure is the number of correct responses.

The BAC composite score for each participant at a given timepoint is computed by taking the sum of the six scaled test scores and dividing by the standard deviation of the sum of the scaled scores from the index population.

11.4.6. Personal and Social Performance Scale (PSP)

The PSP is a 100-point single-item rating scale of personal and social functioning (Morosini-2000). The rating is based on the assessment of a patient's functioning in four areas: 1) socially useful activities; 2) personal and social relationships; 3) self-care; and 4) disturbing and aggressive behaviors. Higher scores indicate better functioning. Scores of 0-30 indicate poor functioning; scores of 31-70 indicate varying degrees of difficulty; and scores of 71-100 reflect only mild difficulties at most.

11.4.7. University of California San Diego (UCSD) Performance-Based Skills Assessment, Brief Version (UPSA-B)

The UPSA-B assesses everyday functioning in persons with serious mental illness (Mausbach-2007). The UPSA-B consists of 2 subscales (communication and financial). The UPSA-B is a measure of functional capacity in which patients are asked to role-play tasks in 2 areas of functioning: (1) communication and (2) finances. The UPSA-Brief requires approximately 10 – 15 minutes to complete and will be administered by a trained professional.

The raw score of the financial subscale ranges from 0 to 11 and the raw score of communication subscale ranges from 0 to 9. Each subscale score is calculated by dividing the raw score by the highest possible raw score of that subscale and then multiplying by 50, so both subscale scores range from 0 to 50. The UPSA-B total score, calculated as the sum of two subscale scores, ranges from 0 to 100. Higher scores reflect better performance.

11.4.8. EuroQol 5D (EQ-5D-5L)

The EQ-5D-5L is a self-administered, standardized measure of health states consisting of two parts: a) EQ-5D-5L descriptive system consisting of one question in each of five dimensions (mobility, self-care, pain, usual activities, and anxiety), and b) a 20-cm visual analogue health status rating. In the descriptive system, respondents are asked to choose the level that reflects their "own health state today" for each of the five dimensions. Once the data have been collected and a database created, a scoring function is used to assign a value (ie, EQ-5D-5L index score) to self-reported health states from a set of population-based preference weights. Additionally, the 20-cm visual analog scale (EQ-VAS) has endpoints labeled "best imaginable health state" and "worst imaginable health state" that are anchored at 100 and 0, respectively. Respondents are asked to indicate how they rate their own health by drawing a line from an anchor box to that point on the EQ-VAS which best represents their own health on that day.

11.4.9. Medication Satisfaction Questionnaire (MSQ)

The MSQ is a single-item, patient-rated, rater administered questionnaire that requires the subject to use a 7-point, Likert-type scale to rate how satisfied they are with their current antipsychotic medication (antipsychotic medication taken at the time of screening or within 30 days of screening) (Vernon-2010). The subject will be asked the following question:

- "Overall, how satisfied are you with your current antipsychotic medication"

Subjects will select 1 of 7 potential responses based on their level of satisfaction from (1) extremely dissatisfied to (7) extremely satisfied as follows:

(1) Extremely dissatisfied

(2) Very dissatisfied

(3) Somewhat dissatisfied

(4) Neither dissatisfied nor satisfied

(5) Somewhat satisfied

(6) Very satisfied

(7) Extremely satisfied

11.4.10. Tobacco Use Information

Information regarding the subject's tobacco use will be recorded in the eCRF at Screening and the EOT/ET visit. Data collected will include the type of tobacco used, approximate amount and time period during which tobacco was / is being used.

11.5. Safety Assessments

The Investigator or appropriate designee will review results of safety assessments on a regular basis and the Sponsor or designee must be kept fully informed of any clinically significant findings either at Screening or subsequently during study conduct.

11.5.1. Adverse Events

Adverse events will be collected for each subject. Subjects should be queried in a non-leading manner, without specific prompting (eg, "Has there been any change in your health status since your last visit?"). See Section 12, Safety Reporting.

AEs and SAEs will be monitored throughout the study at all visits.

11.5.2. Clinical Laboratory Tests

The clinical laboratory tests required by protocol are listed in Section 22, Appendix III.

Blood and urine samples will be collected for clinical laboratory tests. For detailed instructions regarding clinical laboratory procedures, sampling, and shipping guidelines refer to the Central Laboratory Instructions Manual. Samples will be processed at a central laboratory to ensure consistency. All clinical laboratories will be College of American Pathologists (CAP), Clinical

Laboratory Improvement Amendments (CLIA) and/or other laboratory certifications or equivalent accreditation documents.

Any POC (point of care) kits that are performed on site by study personnel rather than in a lab- must be CLIA waived and the study center must possess a CLIA certificate of Waiver.

11.5.3. Vital Signs

Blood pressure and pulse rate measurements will be taken in a supine and standing position. Blood pressure and pulse rate should first be taken with the subject in the supine position after resting for ≥ 5 minutes. Blood pressure and pulse rate will be taken again after standing for 2 to 4 minutes. The same arm should be used during each assessment of blood pressure and pulse rate throughout the study. If a subject develops symptoms consistent with orthostatic hypotension (light-headedness, dizziness, or changes in sensorium upon standing) at any point, his or her supine and standing blood pressure and pulse rate should be collected at that time in the manner described above.

Respiratory rate and temperature will also be measured, and all measurements will be recorded in the eCRF.

Height will be measured without shoes only at Visit 1 (Screening). Weight will be measured in street clothes, without shoes and coat/jacket. BMI will be calculated by site staff using the equation BMI = weight [kg]/height [m]^2 at Screening (Visit 1). BMI for all other visits will be derived within the Electronic Data Capture (EDC) system and calculated during statistical analysis. Waist circumference will be measured.

Vital signs will be obtained prior to clinical laboratory collection and performance of an ECG.

Clinically significant vital sign abnormalities at Screening will be captured in the medical history in the CRF. Any clinically significant changes from Screening, as determined by the Investigator, will be noted as AEs in the CRF.

11.5.4. Electrocardiograms (ECGs)

All ECGs will be obtained in the supine position, after the subject has been resting supine for at least 5 minutes. ECGs will be 12-lead with a 10-second rhythm strip. ECGs should be obtained prior to drawing blood samples. All attempts should be made to use the same ECG recorder for all visits within individual subjects. ECGs will be centrally read at a core lab according to established quality assurance procedures for inter/intra reader variability. Refer to Section 20, Appendix I for additional information. ECG parameters to be collected include ventricular heart rate (beats/min), QT interval (msec), PR interval (msec), QRS interval (msec), RR interval (msec), and centrally-read overall ECG interpretation (Normal; Abnormal, insignificant; Abnormal, potentially significant; Abnormal significant) including type of abnormality, if present. QTcF and QTcB will also be reported.

It is the responsibility of the Investigator to perform a safety review of the ECG data for changes from previous assessments and/or emergent cardiac dysfunction, and to determine subjects' eligibility for or continuation in the study. All ECG tracings and over-read reports will be reviewed, signed and dated by the Investigator. The Investigator must determine and note the clinical significance of all abnormal ECGs. The same physician should review all ECG reports for a given subject whenever possible.

Any clinically significant ECG changes from Screening, as determined by the Investigator, will be noted as AEs in the CRF.

ECGs with possibly drug-related or clinically significant abormal findings of uncertain causality will be repeated.

The original ECG tracing will be kept with subject's source documentation. A copy may be collected by the Sponsor.

11.5.5. Physical and Neurological Examination

Complete PEs as well as neurological exams will be performed. The PE includes an assessment of general appearance and a review of systems (dermatologic, head, eyes, ears, nose, mouth/throat/neck, thyroid, lymph nodes, respiratory, cardiovascular, gastrointestinal, extremities, musculoskeletal, neurologic, and psychiatric systems). The neurological exam includes an assessment of general appearance, mental status, cranial nerves, motor system, sensory system, reflexes, coordination, and gait.

All PE and neurological exam findings at Screening will be captured in the medical history in the CRF. Any clinically significant changes from Screening, as determined by the Investigator, will be noted as AEs in the CRF.

11.5.6. Safety Scales

11.5.6.1. Simpson-Angus Scale (SAS)

The SAS is a clinician-rated assessment of neuroleptic-induced Parkinsonism consisting of 10 items. Items are anchor-based, rated on a 5-point scale of severity, and address rigidity, gait (bradykinesia), tremor, akathisia, shoulder shaking, glabellar tap, and salivation (Siddiqui-2009; Simpson-1970). The SAS will be administered by a qualified rater at the site.

11.5.6.2. Barnes Akathisia Rating Scale (BARS)

The BARS is a rating scale geared toward assessment of neuroleptic-induced akathisia, though it can be used to measure akathisia associated with other drugs as well. The BARS consists of four items, including one item assessing objective restlessness, two items targeting subjective restlessness (awareness and related distress), and one global clinical assessment item. All items are anchored and utilize a 4-point scale, except for the global rating which has a 6-point scale (from absence of akathisia through severe akathisia). The subjective and objective items are summed to yield a total score. The BARS can be administered in about 10 minutes (Barnes-1989; Barnes-2003). The BARS will be administered by a qualified rater at the site.

11.5.6.3. Abnormal Involuntary Movement Scale (AIMS)

The AIMS is a clinician-rated assessment of abnormal movements consisting of unobtrusive observation of the subject at rest (with shoes removed) and several questions or instructions directed toward the subject. Using a severity scale ranging from 0 (none) to 4 (severe), clinicians rate dyskinesia in several body regions, including the facial area, extremities, and trunk. There are two items related to dental status, as well as three global impression items assessing overall severity, incapacitation, and the subject's awareness of abnormal movements (Guy-1976; Munetz-1988). The AIMS raters will be required to meet specific credential and educational

criteria before they are certified to rate for this study. The AIMS will be administered by a qualified rater at the site.

11.5.6.4. Columbia Suicide Severity Rating Scale (C-SSRS)

The C-SSRS is a tool designed to systematically assess and track suicidal adverse events (suicidal behavior and suicidal ideation) throughout the trial. The strength of this suicide classification system is in its ability to comprehensively identify suicidal events while limiting the over-identification of suicidal behavior. The scale takes approximately 5 minutes to administer (Posner-2007). The C-SSRS will be administered by a trained rater at the site. Subjects with Type 4 or Type 5 suicidal ideation during the study will be discontinued from the study and referred to a mental health professional. At screening visit, "Baseline/Screening" version of C-SSRS will be used. For all visits from Visit 2 onward, the "Since Last Visit" version of the C-SSRS will be used.

If a subject answers "yes" to "Suicidal Ideation" Item 4 (active suicidal ideation with some intent to act, without specific plan) or Item 5 (active suicidal ideation with specific plan and intent) on any post-Baseline C-SSRS assessment, an associated AE must be reported.

11.5.6.5. Pittsburg Sleep Quality Index (PSQI)

The Pittsburgh Sleep Quality Index (PSQI) consists of 19 self-rated questions used to measure the quality and patterns of sleep in adults. It differentiates "poor" from "good" sleep quality by measuring seven areas (components): subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleeping medications, and daytime dysfunction over the last month (Buysse-1989).

CCI

[redacted]

11.8. Study Visits and Assessments

See Table 2, for a summary of procedures at each study visit. See Section 11.1 to Section 11.7 for detailed information on conducting assessments.

It is suggested that rating scales be completed in the following sequence, if possible.

Screening Visit	Visits 2 through Visit 9/Early Termination	Visit 10
1. SCID-CT	1. PANSS	1.C-SSRS
2. PANSS	2. BNSS	
3. C-SSRS	3. MADRS	
4. MSQ	4. C-SSRS	
5. CGI-S	5. SAS/BARS/AIMS (Visits 2 and 9 only)	
	6. PSQI (Visits 2 and 9 only)	
	7. PSP (Visits 2 and 9 only)	
	8. EQ-5D-5L (Visits 2 and 9 only)	
	9. BACS (Visits 2 and 9 only)	
	10. UPSA-B (Visits 2 and 9 only)	
	11. MSQ (Visits 1 and 9 only)	
	12. Healthcare resource utilization (Visit 2 only)	
	13. CGI-S	

Note: With the exception of SCID-CT, UPSA-B, Healthcare resource utilization and C-SSRS all rating assessments will be performed by the rater or subject using an electronic tablet. In the event that the electronic tablet is not available, the rating assessments will be performed by the rater or subject using a paper version of the assessment, with the exception of the EQ-5D-5L which is licensed only for electronic use.

11.8.1. Screening: Visit 1 (Day -14 to -1); Inpatient or Outpatient

After a subject provides consent, a unique subject number will be assigned at screening by the IWRS, consisting of a 3-digit protocol number, 3-digit site number, and a unique 3-digit subject identifier (eg, the second screened subject from site #005 will be 301005002). Subjects will be numbered consecutively. No subject numbers are to be reused once assigned. This number will track a subject throughout their participation in the study.

Subjects will be evaluated at the Screening Visit to determine their eligibility for the study. The subject's eligibility assessment will be reviewed by the contract research organization's (CRO) oversight quality team along with the sponsor based on protocol specified inclusion and exclusion criteria. In the event the CRO/sponsor and site do not agree on a subject's eligibility then the subject will not be enrolled.

Subjects found to be ineligible during Visit 1 will not be required to complete all the Visit 1 assessments and will not be followed up on leaving the study.

Subjects who screen fail may be re-screened up to two times, if judged appropriate by the Investigator, after discussion with the Medical Monitor. Re-screened subjects will be re-consented, assigned a new subject number, and all Visit 1 procedures will be repeated.

The Screening Period may be extended for up to 7 days after approval from the Medical Monitor.

The following procedures will be conducted during this visit:

- Obtain signed informed consent and privacy authorization (if applicable or required by local law) from the subject before conducting any other visit procedures, including informed consent for duplicate subject check (US subjects only).

CCI [redacted]

- Review inclusion and exclusion criteria
- Obtain demographic information
- Collect prior and concomitant medications
- Collect adverse events (Note: events occurring prior to first dose of study drug will be identified programmatically as pretreatment events.)
- Collect medical history
- Collect tobacco use information
- Collect psychiatric history
- SCID-CT
- Physical and neurological examination including height and weight; clinical site staff to calculate and record BMI
- Vital sign measurements
- ECG
- Fasted blood samples for clinical laboratory evaluation (hematology and serum chemistry)
- Blood samples for serum pregnancy test (serum human chorionic gonadotropin [β-hCG]) for female subjects and serum follicle stimulating hormone (FSH) for post-menopausal women or if menopause is suspected
- Blood sample for hepatitis screening

- Urine sample for urinalysis and urine drug screen (UDS)
- Duplicate subject check (US sites only)
- PANSS
- C-SSRS
- CGI-S
- MSQ

11.8.2. Baseline: Visit 2 (Day 1); Inpatient

The following procedures will be conducted during this visit:

CCI [redacted]

- Review inclusion and exclusion criteria
- Collect concomitant medications

CCI [redacted]

- Vital sign measurements
- Weight and waist circumference
- Perform standard 12-lead ECG
- Fasted blood samples for clinical laboratory evaluation (hematology and serum chemistry)

CCI [redacted]

- Urine sample for urinalysis, UDS, and β-hCG (for female subjects)
- PANSS
- BNSS
- MADRS
- C-SSRS
- CGI-S
- SAS
- BARS
- AIMS
- PSQI
- PSP
- EQ-5D-5L

- BACS
- UPSA-B
- Healthcare resource utilization
- Collect adverse events (Note: event occurring prior to first dose [on Day 1] of study drug will be identified programmatically as pretreatment events.)
- Randomize to treatment
- Dispense study drug

11.8.3. Visit 3 (Day 4); Inpatient

The following procedures will be conducted during this visit:

- Collect concomitant medications
- Vital sign measurements
- PANSS
- BNSS
- MADRS
- C-SSRS
- CGI-S
- Collect adverse events

11.8.4. Visit 4 (Week 1; Day 8): Inpatient

The following procedures will be conducted during this visit:

- Collect concomitant medications
- Perform study drug accountability
- CCI [redacted]
- Vital sign measurements
- ECG
- PANSS
- BNSS
- MADRS
- C-SSRS
- CGI-S
- Collect adverse events
- Dispense study drug

11.8.5. Visit 5 (Week 2; Day 15); Inpatient

The following procedures will be conducted during this visit:

- Collect concomitant medications
- Perform study drug accountability
- CCI [redacted]
- Vital sign measurements
- PANSS
- BNSS
- MADRS
- C-SSRS
- CGI-S
- Collect adverse events
- Dispense study drug

11.8.6. Visit 6 (Week 3; Day 22); Inpatient

The following procedures will be conducted during this visit:

- Collect concomitant medications
- Perform study drug accountability
- Vital sign measurements
- Weight and waist circumference
- PANSS
- BNSS
- MADRS
- C-SSRS
- CGI-S
- Collect adverse events
- Dispense study drug

11.8.7. Visit 7 (Week 4; Day 29); Inpatient

The following procedures will be conducted during this visit:

- Collect concomitant medications
- Perform study drug accountability
- Vital sign measurements

- PANSS
- BNSS
- MADRS
- C-SSRS
- CGI-S
- Collect adverse events
- Dispense study drug

11.8.8. Visit 8 (Week 5; Day 36): Inpatient

The following procedures will be conducted during this visit:

- Collect concomitant medications
- Perform study drug accountability
- Vital sign measurements
- PANSS
- BNSS
- MADRS
- C-SSRS
- CGI-S
- Collect adverse events
- Dispense study drug

11.8.9. End of Treatment (EOT) or Early Termination (ET) - Visit 9 (Week 6; Day 43): Inpatient

The following procedures will be conducted during this visit:

- Collect concomitant medications
- Perform study drug accountability
- Physical and neurological examination
- Vital sign measurements
- Weight and waist circumference
- Perform standard 12-lead ECG
- Fasted blood samples for clinical laboratory evaluation (hematology and serum

CCI [redacted]

- Urine sample for urinalysis, UDS, and β-hCG (for female subjects)
- PANSS
- BNSS
- MADRS
- C-SSRS
- CGI-S
- SAS
- BARS
- AIMS
- PSQI
- PSP
- EQ-5D-5L
- BACS
- UPSA-B
- MSQ
- Collect tobacco use information
- Collect adverse events
- Duplicate subject check (US sites only)

At this visit, subjects who have participated throughout the duration of the Treatment Period, up to and including Visit 9 will have the option to enroll and continue treatment in an open-label extension study (Study SEP361-303).

For subjects entering the extension study, the Week 6 Visit in this study (SEP361-302) will serve as the Baseline visit for the extension study (SEP361-303) and subjects will not need to return for further visits in this study.

Subjects who do not enter the extension study will complete the Follow-up Period.

11.8.10. Follow-up - Visit 10 (7 ± 2 days after last dose): Inpatient or Outpatient

All subjects who discontinue early or do not elect to enroll in the open-label extension study (Study SEP361-303) will have a safety Follow-up Visit 7 ± 2 days after their last dose of study drug. This visit may be conducted on an outpatient basis, if the subject met the discharge criteria at Visit 9 (Week 6) as specified in Section 10.6. Upon completion or early discontinuation from the double-blind Treatment Phase, hospitalization for up to an additional 7 days during the Follow-up Period to stabilize the subject may be allowed after prior authorization from the Medical Monitor. Hospitalization during the Follow-up Period for up to 7 days will not be considered as an SAE. Hospitalization during the Follow-up Period that exceeds 7 days will be

reported as an SAE, unless the additional hospitalization is due to social reasons (eg, subject lacks transportation to living environment or lacks stable living environment).

The following procedures will be conducted during this visit:

- Concomitant medications
- Physical and neurological examinations
- Vital sign measurements
- Urine sample for β-hCG (for female subjects)
- C-SSRS
- Adverse events

12. SAFETY REPORTING

12.1. Definitions

12.1.1. Adverse Events

An adverse event (AE) is any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related.

Untoward medical occurrences that occur between the time of signing the informed consent form (ICF) and first drug administration are pre-treatment events. Those that occur after first administration of study drug are considered AEs.

An AE can, therefore, be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease occurring after the administration of a medicinal (investigational) product, whether or not considered related to the medicinal (investigational) product. AEs may include the onset of new illness and the exacerbation of pre-existing conditions. AEs will be collected from the signing of the ICF to the last study visit (Visit 10 [Follow-up Visit]).

The Investigator should attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. In such cases, the diagnosis should be documented as the AE and not the individual signs/symptoms.

If a subject answers "yes" to "Suicidal Ideation" Item 4 (active suicidal ideation with some intent to act, without specific plan) or Item 5 (active suicidal ideation with specific plan and intent) on any post-Baseline C-SSRS assessment, an associated AE must be reported.

12.1.2. Serious Adverse Events

A serious adverse event (SAE) is an AE that meets one or more of the following criteria:

- Results in death.
- Is life-threatening.
- Requires hospitalization or prolongation of existing hospitalization.
- Results in persistent or significant disability or incapacity.
- Is a congenital anomaly or birth defect.
- Is an important medical event that may jeopardize the subject or may require a medical or surgical intervention to prevent one of the outcomes listed above. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization.

The term "severe" is often used to describe the severity of a specific event (as in mild, moderate, or severe myocardial infarction) (see Section 12.3); the event itself, however, may be of relatively minor medical significance (such as severe headache). This is not the same as "serious," which is based on subject/event outcome or action criteria usually associated with events that pose a threat to a subject's life or functioning as defined by the criteria above.

During the study, if a subject has a hospitalization or procedure (eg, elective surgery) that was scheduled before the study entry, ie, before informed consent for an event/condition that occurred before the study, the hospitalization is considered a therapeutic intervention and not the result of a SAE. However, if the event/condition worsens during the study, it should be reported as an AE (or SAE, if the event/condition results in a serious outcome such as prolongation of hospitalization).

Life-threatening means that the subject was, in the view of the Investigator, at immediate risk of death from the event as it occurred. This definition does not include an event that had it occurred in a more severe form might have caused death.

SAE criteria information will be captured on the CRF.

12.2. Objective Findings

Any clinically significant changes from Screening in objective findings (eg, clinical laboratory value, ECG value, vital sign values and physical / neurological examination observation), as determined by the Investigator, will be recorded as AEs.

When a clear diagnosis is available that explains the objective findings, this diagnosis will be recorded as the AE, and not the abnormal objective finding (eg, viral hepatitis will be recorded as the AE, not transaminase elevation). If a definite diagnosis is not available, then record the sign (eg, clinically significant elevation of transaminase levels) or symptom (eg, abdominal pain) as the AE.

Clinical laboratory test results and ECG tracings and over-read reports will be reviewed, signed and dated by the Investigator. The Investigator must determine the clinical significance of all out of range values for clinical laboratory tests and all abnormal ECG findings.

Any clinical laboratory value outside the normal range and any centrally over-read abnormal ECG finding will be flagged for the attention of the Investigator or appropriate designee at the study center. The Investigator or appropriate designee will indicate whether the value/finding is of clinical significance. Subjects with any clinically significant abnormal laboratory value(s) or ECG finding at Screening will **not** be allowed into the study (see Section 8.2). Retesting is allowed during the Screening Period and the retest used to determine eligibility after approval from the Medical Monitor; however, the Screening Period will not be extended to accommodate repeat laboratory / ECG tests unless repeat tests are needed due to a technical issue with laboratory sample processing, shipment or testing delay at the central laboratory. If a clinically significant laboratory or ECG abnormality is found after Screening, during the study, and/or at the Follow-Up Visit, this should be recorded as an AE and the subject will be followed until the test(s) has (have) normalised or stabilised. Possibly drug-related or clinically relevant abnormal values of uncertain causality must be repeated. Additional laboratory and ECG testing during the study may be performed if medically indicated.

12.3. Collection and Recording of Adverse Events

All pre-treatment events and AEs must be recorded in the subject's study records/source documents in accordance with the Investigator's normal clinical practice. Pre-treatment events and AEs and SAEs that occur from the signing of informed consent to the subject's last study

visit must be recorded on the CRF. Determination of whether an event is a pre-treatment event, or an adverse event will be made programmatically by the Sponsor or designee, not by the site.

All AEs will be followed until resolution, stabilization of the condition, the event is otherwise explained, or the subject is lost to follow-up.

Each AE is to be evaluated for duration, severity, frequency, seriousness, action taken with the study treatment, outcome, and causal relationship to the study treatment. Additional information will be collected for the non-serious psychiatric AEs that led to discontinuation from the study as well as all serious psychiatric AEs within the study. Definitions for severity, frequency, action taken with the study treatment, outcome, and causal relationship to the study treatment are presented below.

The severity of AE:

- **Mild** - Ordinarily transient symptoms that do not influence performance of subject's daily activities. Other treatment is not ordinarily indicated.
- **Moderate** - Marked symptoms sufficient to make the subject uncomfortable. Moderate influence on performance of subject's daily activities. Other treatment may be necessary.
- **Severe** - Symptoms cause considerable discomfort. Substantial influence on subject's daily activities. May be unable to continue the study, and other treatment may be necessary.

The frequency of AE:

- **Once** – an isolated episode.
- **Intermittent** – occurs on two or more separate occasions.
- **Continuous** – does not abate from date of onset to date of resolution.

The action taken with the study treatment:

- **Drug Interrupted** – Study drug stopped temporarily.
- **Drug Withdrawn** – Study drug stopped permanently.
- **Dose Not Changed**
- **Not Applicable**
- **Unknown**

The outcome of the AE:

- **Recovered/Resolved**
- **Recovering/Resolving**
- **Not Recovered/Not Resolved**
- **Recovered/Resolved with Sequelae**
- **Fatal**

- **Unknown**

The causal relationship of the AE to the study treatment:

- **Not related**
  - **Not related** - Improbable temporal relationship and is plausibly related to other drugs or underlying disease.
- **Related**
  - **Possible** - occurred in a reasonable time after study drug administration but could be related to concurrent drugs or underlying disease.
  - **Probable** - occurred in a reasonable time after study drug administration, is unlikely to be attributable to concurrent drugs or underlying disease, and there is a plausible mechanism to implicate the study drug.
  - **Definite** - occurred in a reasonable time after study drug administration and cannot be explained by concurrent drugs or underlying disease. The adverse event should respond to dechallenge/rechallenge however, this is not mandatory before assigning a definite causality.

The Medical Monitor is the initial contact person for protocol related questions or discussion of AEs. The contact information for the Medical Monitor as well as other emergency contact information can be found in Table 1 of this protocol.

12.4. Immediately Reportable Events

The following medical events must be immediately reported to the Sponsor:

- SAE
- Pregnancy

Emergency contact information can be found in Table 1.

12.4.1. Serious Adverse Event

If the Investigator or study center staff becomes aware of a SAE that occurs in a study subject after first administration of study drug through 30 days following the last dose of the study drug, this must be reported immediately to the Sponsor whether considered related or unrelated to the study drug. SAEs that occur from the signing of the ICF up to the last visit must be recorded on the CRF and the data recorded should agree with that on the SAE form. In addition, pretreatment events that meet the definition of serious (Section 12.1.2) should be reported following the same guidelines.

Should the Investigator become aware of an SAE greater than 30 days post last dose, the Investigator or an authorized delegate should report SAEs "spontaneously" to PPD-PVG if considered at least possibly related to the study drug.

SAEs will be followed until resolution, loss to follow-up, stabilization of condition, or the event is otherwise explained.

An initial or follow-up SAE form as applicable must be completed and signed and sent via fax or email (see Table 1) to PPD-PVG immediately but not more than 24 hours after the Investigator or study center staff become aware of the event. The SAE form must be signed by the Investigator or appropriate designee. The Sponsor provides the SAE form used to report SAEs.

The Sponsor or designee will promptly notify all study centers and Investigators of an SAE that is determined to be expedited to the Regulatory Authorities in accordance with applicable law(s) and regulation(s). These SAEs must be promptly reported to the Institutional Review Board (IRB) or Independent Ethics Committee (IEC) by the Investigator or the appropriate person at the study center if required per IRB/IEC guidelines.

12.4.2. Pregnancy

Pregnancies that occur from the time that informed consent is signed through 90 days following the last dose of the study medication will be collected and reported on the Pregnancy Event Form.

If a subject becomes pregnant during the course of the study, she will be instructed to commence discontinuation of the study medication. Further, the subject will be instructed to return to the study center within 48 hours of the first notification of pregnancy and undergo a serum pregnancy test, as confirmation of pregnancy. If positive, the female pregnant subject will no longer receive any additional study medication. All pregnancies, whether or not the subject received any additional study medication, will be followed until resolution (ie, termination [voluntary or spontaneous] or birth).

If a pregnancy is reported for a study subject's partner from time of subject's first dose to 30 days post last dose, the subject's partner may be asked to sign a consent form to allow the Sponsor to follow her pregnancy. The Sponsor's representative will provide instructions on how to collect pregnancy information in accordance with local requirements. Proper consent to collect the partner's information will be obtained before the collection of any information.

To report a pregnancy, the Pregnancy Event Form must be completed and sent via fax to PPD-PVG immediately but no more than 24 hours after the Investigator or study center staff becomes aware of the pregnancy. The Sponsor provides the Pregnancy Event Form.

If the subject received blinded study medication, unblinding of the study medication will be offered to the subject when knowledge of such treatment may have an impact on further treatment decisions. Otherwise, information regarding to what treatment the subject was assigned may be provided when the study has ended.

Pregnancy itself is not regarded as an AE unless there is a suspicion that the study drug may have interfered with the effectiveness of a contraceptive medication or other AEs were detected.

12.5. Data Monitoring Committee/Data and Safety Monitoring Board

A Data and Safety Monitoring Board (DSMB) will review safety data approximately 3 times annually. The DSMB will be independent of the Sponsor, study CRO, and the Investigators and will be empowered to recommend stopping the study due to safety concerns, but not for efficacy or futility. The DSMB may review blinded, unblinded, or partially unblinded data, but the Sponsor (with the exception of the relevant members of the pharmacovigilance team responsible for reporting Suspected Unexpected Serious Adverse Reactions [SUSARs]), study CRO, and the

Investigators will remain blinded until the official unblinding of the database. The membership of the DSMB and its mandate will be described in a separate DSMB charter.

13. TERMINATION OF SUBJECT FROM STUDY

13.1. Criteria for Subject Termination

Subjects may be discontinued from study participation / the study drug at any time for any of the following reasons. The possible reasons for termination of study participation / study drug are as follows:

- Adverse event
- Lack of efficacy (specify; eg, no improvement in underlying condition)
- Lost to follow-up (specify)
- Withdrawal by subject (specify)
- Non-compliance with study drug (specify)
- Protocol deviation (specify)
- Death
- Pregnancy
- Other (specify)

If at any time during the course of the study, in the opinion of the Investigator, the subject may no longer safely participate due to a change in medical status (eg, experiences an AE, becomes pregnant), the subject must be discontinued from the study drug. Subjects discontinued from study drug will be discontinued from the study.

The reason for study drug discontinuation will be recorded on the appropriate CRF. In case of death, the date of death should be captured on the CRF.

Subjects who prematurely terminate the study participation will not be replaced.

13.2. Clinical Assessments After Study Drug Discontinuation

Subjects who have not received any study drug will not be followed up on leaving the study.

For subjects who have received study drug and who prematurely discontinue from the study treatment (ie, do not complete through Visit 9), every effort should be made to complete the final evaluation procedures, in accordance with the early termination (ET) visit described in Section 11.8.9.

Subjects who complete the study but do not elect to enroll in the open-label extension study (Study SEP361-303) and those subjects who discontinue the study early will complete a follow up visit 7 (±2) days after the last dose of study drug as described in Section 11.8.10.

14. STUDY TERMINATION

The Sponsor reserves the right to discontinue the study at this study center or at multiple centers for safety or administrative reasons at any time while safeguarding that early termination does not compromise subjects' safety or well-being. In particular, a study center that does not recruit at an acceptable rate may be closed. Should the study be terminated, and/or the study center closed for whatever reason, all documentation and study medication pertaining to the study must be returned to the Sponsor or its representative.

If, in the opinion of the Investigator, clinical observations suggest it may be unsafe to continue, the Investigator may terminate part or the entire study after consultation with the Sponsor.

In the event of study or site termination, subjects undergo final evaluation procedures in accordance with the early termination (ET) visit described in Section 11.8.9 and safety Follow-up Visit as described in Section 11.8.10.

15. STATISTICS

15.1. Sample Size

A total of 369 subjects (123 per treatment group: SEP-363856 75 mg/day, SEP-363856 100 mg/day, and placebo) with a global 2-sided alpha of 0.05 will provide 90% power to reject the null hypothesis of no difference in the mean primary efficacy endpoint against placebo for at least one SEP-363856 dose level and 75% power to reject the null hypothesis for both SEP-363856 dose levels using a truncated Hochberg ($\gamma = 0.9$) procedure, assuming a treatment effect size of 0.385 for both dose levels. A clinically meaningful effect size of 0.385 was estimated based on results from Study SEP361-201 and review of published studies of other antipsychotics for the short-term treatment of schizophrenia. The observed effect size in Study SEP361-201 was 0.45 after four weeks of flexible dosing with SEP-363856 at 50 or 75 mg/day. An upward adjustment of approximately 25% is used to compensate for information lost due to subjects who are randomized but drop out and are without complete efficacy data at all scheduled visits. The total sample size will be 462 subjects randomized in 1:1:1 allocation ratio (or 154 subjects per treatment group). CCI [redacted]

15.2. Analysis Populations

15.2.1. Modified Intention-to-Treat Population

The modified intention-to-treat (mITT) population will consist of all subjects who are randomized, have received at least one dose of study drug, and have a Baseline and at least one post-Baseline efficacy measurement in PANSS or CGI-S. Subjects will be included in the mITT population regardless of any protocol deviation. The mITT population will be the primary population for the efficacy analyses. Subjects will be analyzed according to the treatment to which they are randomized.

15.2.2. Per Protocol Population

The per protocol (PP) population will consist of all mITT population subjects who satisfy the following conditions:

- Have 14 days or more overall exposure to study drug
- Did not receive benzodiazepines or hypnotics within 8 hours of Baseline or Visit 9 (Week 6) PANSS assessment
- Have no important protocol deviations, determined by blinded data reviews prior to database lock

Selected efficacy endpoints will be analyzed using the PP population. Subjects will be analyzed according to the treatment to which they are randomized.

15.2.3. Safety Population

The safety population will consist of all subjects who are randomized and have received at least one dose of study drug. Safety population will be the primary population for the safety analyses. Subjects will be analyzed according to the actual treatment received.

15.3. Data Analysis

15.3.1. Subject Disposition

Subject disposition will be summarized by the randomized treatment group (if applicable) and overall for all subjects. The number and percentage of subjects who are screened, screen-failed, randomized, received study drug, and completed or discontinued early from the double-blind Treatment Period (including reasons for discontinuation) will be presented. In addition, the number and percentage of subjects who will roll over to the open-label extension study (SEP361-303) in each treatment group and overall will be presented.

15.3.2. Study Drug Exposure and Compliance

Duration of exposure and compliance will be summarized by treatment group for the safety population.

Duration of exposure (in days) will be calculated as: last dose date - first dose date + 1. Duration of exposure will be summarized both as a continuous variable for the double-blind Treatment Period and categorically:

- Number and percentage of subjects with exposure ≥ 1, ≥ 3, ≥ 7, ≥ 14, ≥ 21, ≥ 28, ≥ 35, and ≥ 42 days;
- Number and percentage of subjects with exposure for 1 - 2, 3 - 6, 7 - 13, 14 - 20, 21 - 27, 28 - 34, 35 – 41, and ≥ 42 days

Percent compliance will be calculated overall for the double-blind Treatment Period as: (number of tablets taken / number of tablets should have been taken) × 100%. Non-compliance is defined as less than 75% or more than 125% non-missing compliance for the double-blind Treatment Period. Subjects with missing compliance will not be classified as non-compliant. Compliance will be summarized both as a continuous variable and categorically (ie, number and percentage of subjects with compliance < 75%, 75% - 125%, > 125%, and missing).

Mean daily dose will be calculated for the entire double-blind Treatment Period as the cumulative dose (mg) of SEP-363856 divided by the duration of exposure (in days), where cumulative dose is the sum of all doses a subject received during the double-blind Treatment Period. Modal daily dose will be determined as the daily dose that is taken for the most time (in terms of number of days) among all doses taken. Both mean daily dose and modal daily dose will be summarized.

The number and percentage of subjects who had a dose reduction during the double-blind Treatment Period will be summarized by treatment group for the safety population.

15.3.3. Important Protocol Deviations

Important protocol deviations (IPDs) will be identified and documented based on blinded reviews of data listings and the protocol deviations log. The IPD categories may include, but may not be limited to:

- Did not satisfy important inclusion and/or exclusion criteria
- Received prohibited medication

- Overall double-blind compliance rate < 75% or > 125%.

IPDs will be identified for all randomized subjects and presented in a data listing. The number and percentage of subjects within each IPD category will be summarized for the mITT population.

15.3.4. Demographic and Baseline Characteristics

Basic demographics (eg, age, gender, race, ethnicity, etc.) will be summarized for all screened subjects by randomization status (ie, randomized vs. not randomized). Demographic and baseline characteristics will be summarized for the mITT population, safety population, and PP population.

Medical history will be coded using Medical Dictionary for Regulatory Activities (MedDRA) and will be summarized by treatment for the safety population by presenting the number and percentage of subjects with at least one condition in each system organ class (SOC) and preferred term (PT). Psychiatric history data will also be summarized by treatment for the safety population.

15.3.4.1. Healthcare Resource Utilization

Healthcare resource utilization data will be summarized descriptively by treatment for the safety population. The frequency and percentage of subjects with physician's office visits, ER visits and hospitalizations (overall and those related to schizophrenia) in the past 3 months of Visit 2 will be summarized. Employment status for the past 3 months, length of hospital stays and the average number of hours a caregiver(s) spends helping the subject per week will be summarized using descriptive statistics.

15.3.5. Efficacy Analyses

15.3.5.1. Primary Efficacy Endpoint Analysis

This section describes the primary analysis and supplementary analysis of the primary efficacy endpoint. Sensitivity analyses of this endpoint are described in Section 15.3.11.

The primary efficacy estimand is defined as the difference between each SEP-363856 dose level and placebo in the mean change of PANSS total score from Baseline to Week 6 in acutely psychotic adult subjects with schizophrenia as characterized by the study inclusion/exclusion criteria, in the hypothetical setting where the subjects were able to stay on study and remain on the study treatment for 6 weeks.

The four attributes of the primary efficacy estimand are as follows:

A. Population of interest: acutely psychotic adult subjects with schizophrenia, as characterized by the inclusion/exclusion criteria of the study. For the efficacy analyses, the mITT population will be used to represent the population of interest.

B. Variable (or endpoint) of interest: change from Baseline in PANSS total score to Week 6.

C. Intercurrent event: The intercurrent event that is deemed to have an impact on the interpretation of the variable of interest is early withdrawal from study treatment for any

reason. This intercurrent event will be handled with the hypothetical strategy. That is, the treatment effect of interest concerns the outcomes had all subjects completed 6 weeks of study treatment. The efficacy data after the last on-treatment visit will not be collected as these data are irrelevant to the treatment effect of interest. Rather, these data will be implicitly predicted based on the assumptions about how the data would evolve after treatment withdrawal.

D. Population-level summary for the variable: the difference in the mean change of PANSS total score from Baseline to Week 6.

Justification for the estimand:

The primary efficacy estimand defining the treatment effect of interest uses the hypothetical strategy specified in the International Conference on Harmonization (ICH) E9(R1) Addendum. The primary objective of the study is to assess the symptomatic effect of SEP-363856 compared to placebo in treating acutely psychotic adult subjects with schizophrenia. The estimand, or target of estimation, following the hypothetical strategy is the pharmacological effect seen, had no withdrawals from study treatment occurred. This hypothetical estimand is justifiable in this case, since the focus is on the pharmacological effect of the drug additional to no other effects. Subjects who withdraw from a symptomatic study treatment either could have lost their treatment effect had the subjects not taken any other symptomatic medication after withdrawal, or could have had their treatment effect masked had the subjects taken other symptomatic medications after withdrawal. This means that any observations taken after subjects stop study treatment will most likely not contribute relevant information about the pharmacological effect of the drug. Under the hypothetical strategy, the primary endpoint of the trial could be considered as a combination of the observed responses at Week 6 from on-treatment completers and the implicitly predicted responses at Week 6 for subjects who withdraw from study treatment during the trial based on certain assumptions about how the unobserved efficacy outcome would evolve in the hypothetical setting of no treatment withdrawal.

For the primary analysis of the primary efficacy endpoint, data will be analyzed using a mixed model for repeated measures (MMRM) under the missing-at-random (MAR) assumption. Under this assumption, the efficacy outcome of subjects in each treatment group after early discontinuation will exhibit the same future evolution as subjects in the same group remaining in the study. The MMRM model will include fixed factors for treatment, visit (Day 4, Weeks 1, 2, 3, 4, 5 and 6; as a categorical variable), country, and treatment-by-visit interaction, and include Baseline PANSS total score as a covariate. An unstructured covariance matrix will be used to model the within-subject correlation. Kenward-Roger approximation will be used to calculate the denominator degrees of freedom. The main estimator of the primary efficacy estimand is the least squares (LS) mean difference in PANSS total score change from Baseline at Week 6 from the primary analysis model of observed repeated measures data.

In case the model above fails to converge, a spatial exponential covariance structure and a spatial power covariance structure will be assumed sequentially. The first covariance structure to yield convergence will be used in the analysis.

The primary analysis of the primary efficacy endpoint will be based on the observed data only. Missing data will not be imputed.

Adjusted p-values will be provided for the comparisons between SEP-363856 treatment groups and placebo on the primary efficacy endpoint, which are related to the Family F1 hypotheses as defined in Section 15.3.5.4.

As a supplementary analysis, change from Baseline in PANSS total score at each scheduled visit and at the Week 6 last-observation-carried-forward (LOCF) endpoints will be analyzed using an analysis of covariance (ANCOVA) model. The model will include factors for treatment and country, and Baseline PANSS total score as a covariate. Additional supplementary analyses will be specified in the statistical analysis plan (SAP).

15.3.5.2. Secondary Efficacy Endpoint Analysis

The primary and supplementary analyses of the secondary efficacy endpoint are described here. Sensitivity analyses of this endpoint are described in Section 15.3.11.

The secondary efficacy estimand is defined as the difference between each SEP-363856 dose level and placebo in the mean change of CGI-S score from Baseline to Week 6 in acutely psychotic adult subjects with schizophrenia as characterized by the study inclusion/exclusion criteria, in the hypothetical setting where the subjects were able to stay on study and remain on the study treatment for 6 weeks. The attributes of this estimand and its justification are similar to those of the primary efficacy estimand described in Section 15.3.5.1.

For the primary analysis of the secondary efficacy endpoint, data will be analyzed using a MMRM model similar to that of the primary efficacy endpoint (see Section 15.3.5.1), with Baseline CGI-S score as the covariate. The primary analysis of this endpoint will be based on the observed data only. Missing data will not be imputed.

Adjusted p-values will be provided for the comparisons between SEP-363856 treatment groups and placebo on the secondary efficacy endpoint, which are related to the Family F2 hypotheses as defined in Section 15.3.5.4.

As a supplementary analysis, change from Baseline in CGI-S score at each scheduled visit and at the Week 6 LOCF endpoint will be analyzed using an ANCOVA model which includes factors for treatment and country, and Baseline CGI-S score as a covariate. Additional supplementary analyses will be specified in the SAP.

15.3.5.3. Analysis of Other Efficacy Endpoints

Change from Baseline in PANSS total score at each scheduled visit except Endpoint (Week 6)

This efficacy endpoint will be analyzed as part of the MMRM model described above for the primary efficacy endpoint (see Section 15.3.5.1).

Change from Baseline in CGI-S score at each scheduled visit except Endpoint (Week 6)

This efficacy endpoint will be analyzed as part of the MMRM model described above for the secondary efficacy endpoint (see Section 15.3.5.2).

Change from Baseline in PANSS subscale scores at each scheduled visit

Change from Baseline in each of the PANSS subscale (positive, negative, and general psychopathology) scores at each scheduled visit will be analyzed using a MMRM model similar to that of the primary efficacy endpoint (see Section 15.3.5.1), with the respective Baseline

subscale score as the covariate. In addition, change from Baseline in each PANSS subscale score at each scheduled visit and at the Week 6 LOCF endpoint will be analyzed using an ANCOVA model which includes factors for treatment and country, and the respective Baseline subscale score as the covariate.

Change from Baseline in BNSS total score at each scheduled visit

Change from Baseline in BNSS total score at each scheduled visit will be analyzed using a MMRM model similar to that of the primary efficacy endpoint (see Section 15.3.5.1), with Baseline BNSS total score as the covariate. In addition, change from Baseline in BNSS total score at each scheduled visit and at the Week 6 LOCF endpoint will be analyzed using an ANCOVA model which includes factors for treatment and country, and Baseline BNSS total score as the covariate.

Change from Baseline in MADRS total score at each scheduled visit

Change from Baseline in MADRS total score at each scheduled visit will be analyzed using a MMRM model similar to that of the primary efficacy endpoint (see Section 15.3.5.1), with Baseline MADRS total score as the covariate. In addition, change from Baseline in MADRS total score at each scheduled visit and at the Week 6 LOCF endpoint will be analyzed using an ANCOVA model which includes factors for treatment and country, and Baseline MADRS total score as the covariate.

PANSS response at each scheduled visit

PANSS response at each scheduled visit is defined as a 20% or greater improvement (ie, decrease) in PANSS total score from Baseline at each scheduled visit. In addition, missing PANSS total score at Week 6 will be imputed by the LOCF method to derive PANSS response at the Week 6 LOCF endpoint.

The percent change in PANSS total score from Baseline will be calculated by:

$$\frac{\text{PANSS total score at a visit or the LOCF endpoint - PANSS total score at Baseline}}{\text{PANSS total score at Baseline - 30}} \times 100\%$$

For each subject, the responder indicator will be set to 1 if the percent change is negative and the magnitude is equal to or greater than 20%. The indicator will be set to 0 if the percentage is negative but the magnitude is less than 20% or if the percentage is non-negative. The indicator will be set to missing if the percentage is missing.

PANSS response at each scheduled visit and at the Week 6 LOCF endpoint will be analyzed using a logistic regression model with responder indicator as the dependent variable and include treatment and geographic region as fixed factors and Baseline PANSS total score as a covariate.

Change from Baseline in BACS composite score at Week 6

Change from Baseline in BACS composite score at Week 6 will be analyzed using an ANCOVA model which includes factors for treatment and country, and Baseline BACS composite score as a covariate.

Change from Baseline in PSP total score at Week 6

Change from Baseline in PSP total score at Week 6 will be analyzed using an ANCOVA model which includes factors for treatment and country, and Baseline PSP total score as a covariate.

Change from Baseline in EQ-5D-5L: visual analog scale (VAS), index value and dimension score

Change from Baseline in EQ-5D-5L VAS and index value at Week 6 will each be analyzed using an ANCOVA model which includes factors for treatment and country, and the respective Baseline score as the covariate.

The number and percentage of subjects reporting each level of problem under each of the 5 dimensions at Baseline and Week 6 (ie, the frequency distribution of the dimension scores) will be summarized descriptively by treatment group.

Change from Baseline in UPSA-B total score at Week 6

Change from Baseline in UPSA-B total score at Week 6 will be analyzed using an ANCOVA model which includes factors for treatment and country, and Baseline UPSA-B total score as a covariate.

Change from Baseline in MSQ score at Week 6

Change from Baseline in MSQ score at Week 6 will be analyzed using an ANCOVA model which includes factors for treatment and country, and Baseline MSQ score as a covariate.

15.3.5.4. Adjustment for Multiplicity

Type I error control will only be performed for the primary analysis of the primary and secondary efficacy endpoints in the mITT population. Nominal p-values will be reported for all other statistical tests.

Multiplicity adjustment will be applied to address the following three sources of multiplicity in this trial:

1) Analysis of the primary endpoint and the secondary efficacy endpoint
2) Analysis of two SEP-363856 dose-placebo comparisons
3) CCI [redacted]

The first two sources of multiplicity will be addressed through a Hochberg-based gatekeeping procedure derived using the enhanced mixture method (Dmitrienko-2011; Dmitrienko-2013; Kordzakhia-2018). The null hypotheses of no difference in treatment effect between each of the SEP-363856 dose levels and placebo associated with the primary and the secondary efficacy endpoint will be grouped into two hierarchical families:

- Family F1: SEP-363856 75 mg/day vs placebo (H1), and SEP-363856 100 mg/day vs placebo (H2), based on change from Baseline in PANSS total score at Week 6 (E1)
- Family F2: SEP-363856 75 mg/day vs placebo (H3), and SEP-363856 100 mg/day vs placebo (H4), based on change from Baseline in CGI-S score at Week 6 (E2)

The truncated Hochberg ($\gamma = 0.9$) procedure will be applied to the hypotheses in Family F1 (H1 and H2) and the regular Hochberg procedure will be applied to the hypotheses in Family F2 (H3

and H4). There is a serial logical restriction among the hypotheses: H3 is testable only if H1 is rejected; H4 is testable only if H2 is rejected.

CCI [redacted] At the final analysis, evidence of treatment effectiveness from Stage 1 data and Stage 2 data will be combined using the marginal combination function approach proposed in Sugitani-2018. Details of the multiplicity adjustment methodology will be provided in the SAP.

15.3.5.5. Subgroup Analysis

Subgroup analysis will be performed on certain subgroups of interest for the primary and secondary efficacy endpoints. The subgroup factors of interest will include age, sex, race, number of prior hospitalizations for treatment of schizophrenia, duration of schizophrenia, geographic region, and country. Details of the subgroup analyses will be described in the SAP.

15.3.6. Safety Analyses

15.3.6.1. Adverse Events

Both AEs and pre-treatment events will be coded using MedDRA.

The following summaries will be provided by treatment and by MedDRA SOC and PT:

- All AEs (including incidence rate and event count)
- AEs by severity (mild, moderate, severe; including incidence rate)
- AEs by relationship to study drug (related, not related; including incidence rate)

The following conventions will be followed in summarizing AEs:

- For incidence rate summaries, each subject will be counted only once within each SOC and within each PT.
- If a subject reports more than one AE within a PT and/or a SOC, the AE with the highest known severity will be used in the by severity summary. AEs with a missing severity will be assigned to the highest severity.
- For summaries by relationship to study drug, AEs will be grouped as "related" or "not related." AEs assessed as "possible," "probable," or "definite," will be grouped as "related." AEs with a missing relationship to study drug will be regarded as related. If a subject reports more than one AE within the same SOC and PT, and any are related, the AE will be summarized as related.

Summaries of serious AEs (SAEs) and AEs leading to discontinuation by treatment will also be provided. In addition, summaries of all AEs, SAEs, and AEs leading to discontinuation by modal daily dose will be provided. All AEs starting after the last dose of the study drug up to 9 days following the last dose will be summarized separately. Data listings of AEs, SAEs, AEs leading to discontinuation, and deaths will be presented.

15.3.6.2. Clinical Laboratory Assessments

Clinical laboratory parameters will be summarized by presenting shift tables and through by visit summaries of the observed values and the change from Baseline values by treatment. For parameters with categorical outcomes, the number and percentage of subjects with each outcome will be summarized by visit. The number and percentage of subjects with at least one potentially clinically significant (PCS) value post Baseline for selected parameters will also be presented. PCS criteria for clinical laboratory parameters will be provided in the SAP.

15.3.6.3. ECGs

ECG analysis will be based on the centrally read data. Observed values and changes from Baseline in ECG parameters will be summarized by treatment. In addition, the number and percentage of subjects with prolonged QTc intervals (> 450 msec, > 480 msec, and > 500 msec) and changes in QTc intervals ≥ 30 but < 60 msec and ≥ 60 msec will be summarized by treatment. Fridericia's correction (QTcF) and Bazett's correction (QTcB) will be used for QT interval correction.

15.3.6.4. Vital Signs

Vital sign parameters will be summarized by presenting by visit summaries of the observed values and the change from Baseline values by treatment. In addition, the number and percentage of subjects with at least one PCS value post Baseline for selected parameters will be presented. PCS criteria for the vital sign parameters will be provided in the SAP.

Orthostatic hypotension is defined as a decrease of ≥ 20 mmHg in systolic blood pressure or ≥ 10 mmHg in diastolic blood pressure after a subject has been standing for at least 2 to 4 minutes, compared to the systolic blood pressure and diastolic pressure measured in the supine position, respectively. Orthostatic tachycardia is defined as a pulse rate increase of ≥ 20 bpm and a pulse rate of > 100 bpm after a subject has been standing for at least 2 to 4 minutes, compared to the pulse rate measured in the supine position.

The number and percentage of subjects with orthostatic hypotension and orthostatic tachycardia will be summarized for Baseline and the overall post-Baseline period, as well as by visit.

15.3.6.5. Physical and Neurological Examination

Any clinically significant physical and neurological examination findings at screening will be captured as medical history and summarized together with the other medical history data. Clinically significant new findings or changes from the screening visit will be captured as AEs as appropriate and summarized together with the other AEs.

15.3.6.6. Concomitant Medications

All medications will be coded to indication-specific Anatomical Therapeutic Chemical (ATC) classification (ie, ATC level 3) and preferred name using the World Health Organization Drug Dictionary (WHO-DD).

Any medications taken during the course of the study, with a start date/time on or after the first dose of study drug and on or before the last dose of study drug; or with a start date/time prior to, and an end date/time on or after, the first dose of study drug, or marked as ongoing, will be

considered concomitant medications. Medications that ended prior to the first dose of study drug will be considered prior medications. Medications that started after the last dose of study drug will not be considered concomitant but will be considered post-treatment. Prior and Concomitant medications will be summarized for the number and percentage of subjects using each medication by treatment and by the drug class and preferred name for the safety population.

15.3.6.7. Suicidality Measure

Frequency and severity of suicidal ideation and suicidal behavior as measured by the C-SSRS scale will be summarized by treatment for the overall post-Baseline period and by visit.

15.3.6.8. Movement Disorder Measures

Movement disorder measures include SAS, BARS and AIMS. Changes from Baseline at Week 6 in SAS mean score, BARS total score and AIMS total score will each be analyzed using an ANCOVA model which includes factors for treatment and country, and the respective Baseline score as the covariate. Additional analyses on the movement disorder scales will be described in the SAP.

15.3.6.9. Pittsburgh Sleep Quality Index

Change from baseline in PSQI global score at Week 6 will be analyzed using an ANCOVA model which includes factors for treatment and country, and Baseline PSQI global score as a covariate.

15.3.6.10. Subgroup Analysis

Selected safety data will be summarized by subgroups of geographic region, sex, age, number of prior hospitalizations for treatment of schizophrenia, and duration of schizophrenia. Details of subgroup analysis of the safety data will be provided in SAP.

CCI [redacted]

CCI [redacted]

CCI [redacted]

CCI

[redacted]

15.3.10. Treatment of Missing Data

For scales with more than one item, such as PANSS and MADRS, if any item score contributing to the total/subscale score is missing, the total/subscale score will be set to missing.

Missing data at Week 6 will be imputed using the LOCF approach for the ANCOVA analyses, where applicable. For the MMRM analyses, no imputation for missing data will be performed unless otherwise specified.

15.3.11. Sensitivity Analyses

This section describes the sensitivity analyses of the primary and secondary efficacy endpoints.

Subjects will be grouped based on the visit at which they discontinue from the study. This will result in eight groups of subjects: Day 4 terminators, Week 1 terminators, Week 2 terminators, Week 3 terminators, Week 4 terminators, Week 5 terminators, Week 6 terminators, and Completers. Mean change from Baseline in PANSS total score and in CGI-S score will be plotted across visits by time of discontinuation and by reason of discontinuation, in order to assess whether these two efficacy measures appear to be correlated with study discontinuation.

The mechanisms that caused missing data may or may not be at random. The MMRM models used in the primary analysis of the primary and secondary efficacy endpoints assume that data are missing at random. In order to assess the robustness of the primary analysis results by deviating away from the MAR assumption, sensitivity analyses, such as a tipping point analysis, a copy reference analysis, and a jump to reference analysis, will be performed on the primary and secondary efficacy endpoints. Details of these analyses will be provided in the SAP.

16. PROCEDURE FOR CLINICAL STUDY QUALITY CONTROL /DATA COLLECTION, MANAGEMENT, AND QUALITY ASSURANCE

16.1. Data Collection/Electronic Data Capture (EDC)

The results from Screening and data collected during the study (except clinical laboratory test results, ECG results, CCI and some scales) will be recorded in the subject's electronic CRF. Data will be entered into source documents prior to being transcribed into the CRF. The study centers will use an EDC system that is compliant with relevant FDA regulatory requirements per 21 Code of Federal Regulation (CFR) Part 11. Password protected access to the EDC system will be via a secure website. Data queries and data corrections will be handled through the same system. All transactions within the EDC system are fully documented within an electronic audit trail. Each set of completed CRFs must be reviewed and electronically signed and dated by the Investigator.

16.2. Computerized Systems Used for Source Data

A list of the computerized systems that will be used to create, modify, maintain, archive, retrieve, or transmit source data are presented below, pursuant to the Guidance for Industry Computerized Systems Used in Clinical Investigations, May 2007.

Table 6: Computerized Systems Used for Source Data

Protocol Step	Computerized System Type or Description
Obtain informed consent	A
CCI	
Review inclusion/exclusion criteria	A
Prior/concomitant medication review	A
Randomize (IWRS) to treatment	E
Dispense (IWRS) study drug	E
Study drug accountability	A, E
Demography	A
Medical history	A
Psychiatric history	A
SCID-CT	none
Physical and neurological examination	A
Height	A
Vital sign measurements	A
Weight	A
Waist circumference	A
12-lead Electrocardiogram (ECG)	C
Hematology, chemistry, and urinalysis	B
Serum follicle stimulating hormone (FSH)	B
Serum human chorionic gonadotropin (β-hCG)	B

Table 6: Computerized Systems Used for Source Data (Continued)

Protocol Step	Computerized System Type or Description
CCI [redacted]	
CCI [redacted]	
Urine β-hCG (local)	A
Urine drug screen (central)	B
Positive and Negative Syndrome Scale (PANSS)	F
Clinical Global Impression – Severity (CGI-S)	F
Brief Negative Symptom Scale (BNSS)	F
Montgomery-Asberg Depression Rating Scale (MADRS)	F
Columbia Suicide Severity Rating Scale (C-SSRS)	A
Abnormal Involuntary Movement Scale (AIMS)	F
Barnes Akathisia Rating Scale (BARS)	F
Simpson-Angus Scale (SAS)	F
Pittsburg Sleep Quality Index (PSQI)	F
BACS (BACS)	G
Personal and Social Performance Scale (PSP)	F
UPSA-B	A
EuroQol-5D-5L	F
Medication Satisfaction Questionnaire (MSQ)	F
Healthcare resource utilization	A
Pretreatment/Adverse event (AE) monitoring	A
Statistical analysis	SAS®, version 9.2 or higher

A = EDC (Medidata RAVE); B = Central Lab; C = ECG central vendor; D = LIMS/ASCII; E = IWRS; F = Signant Health; G = VeraSci.

Abbreviations: BACS = Brief Assessment of Cognition in Schizophrenia; EDC = electronic data capture; CDR = clinical data repository; EQ-5D-5L = EuroQol– 5 Dimensions – 5 Levels; IWRS = interactive web response system; LIMS = laboratory information management system; SCID-CT = Structured Clinical Interview for DSM-5, Clinical Trials Version; UPSA-B = University of California San Diego Performance-based Skills Assessment, Brief Version.

16.3. Study Monitoring

This study will be monitored using a risk-based approach from initiation to completion by the Sponsor or its representative. Monitoring will include personal visits and telephone communication to assure that the investigation is conducted according to protocol and in order to comply with International Conference on Harmonization (ICH) Good Clinical Practice (GCP). On-site review of CRFs will include a review of forms for completeness and clarity, and consistency with source documents available for each subject.

16.4. Audits

The study may be subject to audit by the Sponsor/designee. If such an audit occurs, the Investigator must agree to allow access to required subject records. This is dependent on the subject granting consent by signing the ICF. By signing this protocol, the Investigator grants

permission to personnel from the Sponsor or its representatives for on-site monitoring and auditing of all appropriate study documentation, as well as on-site review of the procedures employed in CRF generation, where clinically appropriate.

In accordance with ICH GCP the Sponsor may select this study for audit. During the audit the Sponsor representative will carry out an inspection of center facilities (eg, pharmacy, drug storage areas, laboratory) and review study related records in order to evaluate the study compliance with the Sponsor/center SOPs, protocol, ICH GCP and local regulations. The PI or appropriate designee must also agree to inspection of all study documents by the regulatory authorities and the Independent Ethics Committee (IEC). Should the PI or appropriate designee be notified of a regulatory inspection involving this study they should notify the Sponsor immediately.

16.5. Study Documentation

Study records are comprised of source documents, CRFs, and all other administrative documents, eg, Institutional Review Board (IRB)/IEC correspondence, clinical study materials and supplies shipment manifests, monitoring logs, Sponsor and CRO correspondence, etc. A study specific binder will be provided with instructions for the maintenance of study records.

Source document is defined as any handwritten or computer-generated document that contains medical information or test results that have been collected for or are in support of the protocol specifications, eg, clinical laboratory reports, clinic notes, drug disbursement log, subject sign in sheets, subject completed questionnaires if applicable, telephone logs, ECGs, etc. All draft, preliminary and pre-final iterations of a final report are also considered to be source documents, eg, faxed laboratory reports and hard copy laboratory reports, faxed initial results and hard copy, final report.

16.6. Clinical Laboratory Certification and Normal Values

A central laboratory will be used for analysis of the clinical laboratory tests for this study. The central laboratory will provide the Investigator, Sponsor/CRO with laboratory certification(s) and a dated copy of normal range values for the central clinical laboratory selected to analyze clinical specimens. If an exception is granted to use a local laboratory, the Investigator must supply the Sponsor/CRO with laboratory certification, lab director's curricula vitae and a current, dated copy of normal range values.

17. ETHICAL AND REGULATORY OBLIGATIONS

17.1. Study Conduct

The Investigator agrees that the study will be conducted according to the protocol, ICH Good Clinical Practice (GCP), ICH guidelines and the ethical principles that have their origin in the Declaration of Helsinki. The Investigator will conduct all aspects of the study in accordance with applicable local law(s) and regulation(s).

The Investigator will assure proper implementation and conduct of the study including those study-related duties delegated to other appropriately qualified individuals. The Investigator will assure that study staff cooperate with monitoring and audits.

The Investigator must sign and return to Sponsor/CRO the "Investigator Approval" page.

The Investigator must provide a copy of current curriculum vitae (including a copy of a current medical license, where applicable) and financial disclosure information. In countries where medical licensure is not issued, the following documentation is acceptable, as applicable:

- Registration number/stamp with a registration number stated on curriculum vitae.
- Appropriate diploma number stated on curriculum vitae.
- Copy of the diploma.

The Investigator must sign and return a completed Form FDA 1572 "Statement of Investigator" to Sponsor/CRO.

17.2. Institutional Review Board/Independent Ethics Committee

Documented approval for conducting the study from appropriate Institutional Review Board (IRB)/Independent Ethics Committee (IEC) will be obtained for all participating study centers prior to initiation of the study, according to ICH GCP, applicable local law(s) and regulation(s). When necessary, an extension, amendment or renewal of the IRB/IEC approval must be obtained and also forwarded to the Sponsor. The IRB/IEC must supply the Sponsor a list of the IRB/IEC membership, and a statement to confirm that the IRB/IEC is organized and operates according to ICH GCP, applicable law(s) and regulation(s).

A copy of written IRB/IEC approval or favorable opinion of the protocol, informed consent form and subject recruitment material (if applicable) must be provided to Sponsor/CRO prior to start of the study. The approval or favorable opinion letter must be signed by the IRB/IEC chairman or designee identify the IRB/IEC name and address, identify the clinical protocol by title and/or protocol number, and include the date that approval or favorable opinion was granted. The letter must also contain a statement that the IRB/IEC complies with the requirements in 21 CFR Part 56 for a study conducted under a US investigation new drug (IND) or ICH GCP, as applicable.

The Investigator/CRO is responsible for obtaining from the IRB/IEC continued review of the clinical research or submitting periodic progress reports, in accordance with applicable regulations, at intervals not to exceed one year and (if applicable) as otherwise additionally specified by the IRB/IEC. The Sponsor must be supplied with written documentation of continued review of the clinical research.

The Investigator must promptly inform their IRB/IEC of all SAEs reported by subjects enrolled in the study or other safety information reported from Sponsor/CRO in accordance with applicable law(s) and regulation(s).

17.3. Informed Consent

The informed consent form will be approved by the Sponsor/CRO prior to submission to the IRB/IEC. The Sponsor/CRO may provide a template informed consent form to be qualified by each research facility to conform to local requirements. All informed consent forms must contain the minimum elements as mandated by ICH GCP, applicable local law(s) and regulations and will be subject to Sponsor/CRO approval as well as IRB/IEC approval. The Sponsor/CRO may submit informed consent forms to a central IRB/IEC for review and approval or favorable opinion contingent upon prior Investigator permission and review.

Before recruitment and enrollment, each prospective subject will be given a full explanation of the study, allowed to read the approved informed consent form and be provided ample time and the opportunity to ask any questions that may arise. Once all questions have been answered and the Investigator is assured that the prospective subject understands the implications of participating in the study, the prospective subject will be asked to give consent to participate in the study by signing the informed consent form. As part of the consent process, each prospective subject must consent to direct access to his/her medical records for study-related monitoring, auditing, IRB/IEC review, and regulatory inspection. It should be clearly explained to each prospective subject that participation in each and every clinical visit and assessment is expected. The subject may be discontinued from study medication, but that does not necessarily negate the expectation that the subject will continue to participate in the study through the final visit/assessment. The Investigator will provide a copy of the signed informed consent form to each subject and will record the date of the informed consent on the CRF.

If an amendment to the protocol changes the subject participation schedule in scope or activity, or if important new information becomes available that may be relevant to the subject's consent, the informed consent form must be revised, submitted to the IRB/IEC for review and approval or favorable opinion. The revised informed consent form must be used to obtain consent from a subject currently enrolled in the study if he or she is affected by the amendment. The revised informed consent form must be used to obtain consent from any new subjects who are enrolled into the study after the date of the approval or favorable opinion of the protocol amendment.

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17.4. Subject Privacy

The Sponsor (or Sponsor representative) or any designees affirm uphold the subjects' confidentiality. The subject will be identified by unique code only; full names will be masked prior to transmission to the Sponsor. The confidentiality of the subject's personal data shall be protected in accordance with appropriate laws and regulations.

If any cases are identified where the subject's confidentiality has been breached, this must be rectified immediately. All subject identifiable information should be removed, and the Sponsor notified.

17.5. Protocol Amendments and Emergency Deviations

All revisions and/or amendments to this protocol must be approved in writing by the Sponsor and the appropriate IRB/IEC. The Investigator will not make any changes to the conduct of the study or the protocol without first obtaining written approval from the Sponsor and the IRB/IEC, except where necessary to eliminate an apparent immediate hazard to a study subject.

Emergency deviations or modifications may be initiated without Sponsor or IRB/IEC approval or favorable opinion, only in cases where the deviation or modification is necessary to eliminate or avoid an immediate apparent hazard to subjects. Emergency deviations or modifications must be reported to the Sponsor/CRO and the IRB/IEC immediately, or in accordance with applicable regulatory requirements.

17.6. Records Retention

The Investigator/the study center must arrange for retention of study records at the study center for at least 15 years (or at least 25 years in the EU) from time of participation in the study or longer in accordance with applicable regulations and Sponsor SOPs. The Investigator/site should take measures to prevent accidental or premature destruction of these documents. Documents cannot be destroyed without written Sponsor authorization. The Sponsor will inform the Investigator/the study center when the destruction of documents is permitted.

17.7. Inspection of Records

In the event of an inspection, the Investigator agrees to allow representatives of the Sponsor and its representative and, the regulatory authorities' access to all study records. The Investigator will promptly notify the Sponsor/CRO of all requests to inspect a Sunovion-sponsored study by government agencies and will promptly forward a copy of all such inspection reports.

17.8. Financial Disclosure

By signing this protocol, the Investigator agrees to provide to the Sponsor prior to start of study accurate financial information to allow the Sponsor to submit complete and accurate certification and disclosure statements as required by the US FDA regulations (21 CFR Part 54). The Investigator further agrees to provide this information on a Financial Disclosure/Certification Form that is provided by the Sponsor. The Investigator will update this information if there are any relevant changes during the conduct of the study and for one year after completion of the study.

The Investigator also consents to the transmission of this information to the Sponsor for these purposes. This may involve the transmission of information to countries that do not have laws protecting personal data.

17.9. Publication Policy

Any formal presentation or publication of data collected as a direct or indirect result of the study will be considered a joint publication by the Investigators and the appropriate personnel of the Sponsor. For multicenter studies, it is mandatory that the first publication is based on all data obtained from all analyses as stipulated in the protocol. Investigators participating in multicenter studies must agree not to present data gathered individually or by a subgroup of centers before the full, initial publication, unless this has been agreed to by all other Investigators and by the Sponsor.

The Sponsor will disclose the study results, in the form of a clinical study report synopsis, to the IEC and the applicable regulatory authorities within one year of the end of the study. The format of this synopsis and that of the clinical study report should comply with ICH E3 guidelines for structure and content of a clinical study report.

Investigators participating in multicenter studies must agree not to present data gathered individually or by a subgroup of centers before the full, initial publication, unless this has been agreed to by all other Investigators and by the Sponsor.

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19. INVESTIGATOR APPROVAL

I have read the protocol, SEP361-302, Version 4.00 "A Randomized, Double-blind, Parallel-group, Placebo-controlled, Fixed-dose, Multicenter Study to Evaluate the Efficacy and Safety of SEP-363856 in Acutely Psychotic Subjects with Schizophrenia", and agree that it contains all necessary details for conducting the study and to conduct the study in strict accordance with the specifications outlined herein.

I agree that no additional procedure(s) will be added during the conduct of the study except through protocol amendment by Sunovion Pharmaceuticals Inc. and after documentation of IRB approval.

Investigator Signature: _____

Print Investigator Name: _____

Date: _____

20. APPENDIX I. CARDIAC SAFETY MONITORING (ECG)

1. Requirements for Testing

ECG equipment and supplies will be provided by the centralized cardiac safety vendor and should be used for all in-clinic protocol ECG assessments.

- All 12-lead ECGs will be recorded in the same manner.
- The study center personnel must be adequately trained in performing ECGs on the specific ECG equipment used in this protocol that is provided by the cardiac safety vendor.
- To the extent possible, the same ECG machine and personnel should be used to acquire a subject's ECGs throughout the period of their participation in the study.
- ECGs will be recorded with at least one 10-second single-lead tracing recorded from Lead II.

2. Subject Restrictions and Instructions

- Prior to ECG acquisition, the subject will have rested at least 5 minutes in the supine position and will remain so until the ECG is obtained.

3. Reporting

- It is the responsibility of the Investigator to perform a safety review of the ECG data for changes from previous assessments and/or emergent cardiac dysfunction, and to determine subjects' eligibility or continuance in the study.
- ECGs will be reviewed, signed and dated by the Investigator listed on the Form FDA 1572 (MD or DO) after each ECG collection. The same Investigator should review all ECG reports for a given subject whenever possible.
- For all ECGs, a report will be provided by the cardiac safety vendor to the study center for review and signature.
- The ECG tracing will be kept with subject's source documentation and / or CRF unless it is specified otherwise. The original ECG and the cardiologist's over-read will be retained at the study center.

4. Data Standardization

ECG data will be transmitted to a centralized cardiac safety vendor and centrally over-read and interpreted using standardized procedures.

21. APPENDIX II. HALOPERIDOL EQUIVALENT DOSES

Medications	Haloperidol Equivalent (12 mg)
Typical Antipsychotics	
Chlorpromazine	600 mg
Chlorprothixene	500 mg
Fluphenazine	15 mg
Haloperidol	12 mg
Perphenazine	40 mg
Thioridazine	500 mg
Thiothixene	30 mg
Trifluoperazine	25 mg
Long Acting Antipsychotics	
Aripiprazole maintena	558.6 mg.4 wk
Aripiprazole lauroxil	558.6 mg/4 wk
Clopenthixol decanoate	300 mg/4 wk
Flupenthixol decanoate	40 mg/2-3 wk
Fluphenazine decanoate (mg/2–3 wk)	34 mg/2-3 wk
Fluphenazine enanthate	25 mg
Haloperidol decanoate (mg/4 wk)	159 mg/4 wk
Olanzapine pamoate (mg/4 wks)	405 mg
Paliperidone palmitate (Sustenna®) long acting injectable	234 mg/4 wk
Paliperidone palmitate (Trinza®) long acting injectable	819 mg/12 wk
Perphenazine enanthate	100 mg/2 wk
Pipotiazine palmitate	100 mg/4 wk
Risperidone microspheres	50 mg/2 wk
Zuclopenthixol decanoate	200 mg/2 wk

Medications	Haloperidol Equivalent (12 mg)
Atypical Antipsychotics	
Amisulpride	800
Aripiprazole	30
Asenapine	30
Brexpiprazole	4.5
Cariprazine	4.5
Clozapine	900
Haloperidol	12
Iloperidone	24
Lurasidone	120
Olanzapine	20
Paliperidone	9
Quetiapine	700
Risperidone	6
Sertindole	36
Sulpiride	800
Ziprasidone	160

For antipsychotics not listed in the tables above, please consult the Medical Monitor.

References:

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22. APPENDIX III. CLINICAL LABORATORY TESTS

Detailed instructions will be provided in a study center manual.

The following clinical laboratory tests are to be performed.

Clinical Safety Panel

HEMATOLOGY: (Differential reported as % and absolute value)
Hemoglobin, Hematocrit, Platelet Count, Red blood cell (RBC) Count, White blood cell (WBC) - Total Count, WBC Differential, (Basophils, Eosinophils, Lymphocytes, Monocytes, Neutrophils)

BLOOD CHEMISTRIES: Alanine aminotransferase (ALT), Albumin, Alkaline Phosphatase (ALP), Aspartate aminotransferase (AST), Bicarbonate, Bilirubin (Total, Direct, Indirect), Blood Urea Nitrogen (BUN), Calcium (Ca), Chloride (Cl), Cholesterol, Creatinine, Creatinine clearance (calculated GFR), Creatinine phosphokinase (CPK), Free T3, Free T4, HDL-Cholesterol, hs C-reactive Protein (CRP), Glucose, Hemoglobin A1c (HbA1c), LDL-Cholesterol, Magnesium (Mg), Phosphorus (P), Potassium (K), Prolactin, Protein (Total), Serum Insulin, Sodium (Na), Thyroid stimulating hormone (TSH), Triglycerides, Uric Acid

URINALYSIS: Blood, Glucose, Ketones, Leukocyte esterase, Microscopic examination, Nitrites, pH, Protein

URINE DRUG SCREENING: Amphetamines, Barbiturates, Benzodiazepines, Cannabinoids, Cocaine, Methamphetamines, Methadone, Methylenedioxymethamphetamine (MDMA), Phencyclidine (PCP), Opiates, Oxycodone

SEROLOGY PANEL: Hepatitis B Ag, Hepatitis C Ab

OTHER TESTS: Serum Pregnancy (β-HcG) (in female subjects only), Urine Pregnancy Test (in female subjects only), Follicle stimulating hormone (in female subjects with suspected menopause)

Laboratory reports will be initialed and dated on all pages by the Investigator listed on the Form FDA 1572 (MD or DO). Laboratory test results will be reviewed by the Investigator as they become available. The Investigator must determine the clinical significance of all out-of-range lab values (except drug screens). Possibly drug-related or clinically relevant abnormal values of uncertain causality must be repeated. Any abnormal values that persist should be followed until the test(s) has (have) normalised or stabilised.

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25. APPENDIX VI. MINIMUM PANSS TOTAL SCORE CRITERIA AT BASELINE

The following formula is to be utilized to determine the PANSS total score change at Baseline (Visit 2):

$$\frac{\text{PANSS total score at Baseline - PANSS total score at Screening}}{\text{PANSS total score at Screening - 30}} \times 100\%$$

PANSS total score at Screening (V1)	MINIMUM Permissible PANSS total score at Baseline (V2)
80	80
81	80
82	80
83	80
84	80
85	80
86	80
87	80
88	80
89	80
90	80
91	80
92	80
93	81
94	82
95	83
96	83
97	84
98	85
99	86
100	87
101	87
102	88
103	89

PANSS total score at Screening (V1)	MINIMUM Permissible PANSS total score at Baseline (V2)
104	90
105	91
106	91
107	92
108	93
109	94
110	95
111	95
112	96
113	97
114	98
115	99
116	99
117	100
118	101
119	102
120	103
121	103
122	104
123	105
124	106
125	107
126	107
127	108
128	109
129	110
130	111